THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MAY, 1934.

ORIGINAL ARTICLES.

THE RELATIONSHIP OF POLYCYTHEMIA TO DUODENAL ULCER.*

By William Boyd, M.D., F.R.C.P. (Lond.),

PROFESSOR OF PATHOLOGY, UNIVERSITY OF MANITOBA AND PATHOLOGIST TO THE WINNIPEG GENERAL HOSPITAL, WINNIPEG, CANADA.

To determine the relationship between two abnormal findings which are encountered in the same patient is sometimes a matter of great difficulty. There is the possibility of chance. If a causal relationship is suspected, it may be by no means easy to say which of the deviations from the normal is cause and which is effect. An illustration of the truth of these statements is afforded by the association of polycythemia and chronic duodenal ulcer, of which a certain number of cases have been reported within recent years.

Friedman, in 1913, described 6 cases in which a duodenal ulcer was demonstrated at operation, associated with definite polycythemia. In the only one of these which came to autopsy chronic pancreatitis was found. Friedman at that time stated that the literature did not contain a single reference to the association of erythrocytosis and duodenal ulcer. In 1914 he recorded an additional 11 cases. He believed that both the polycythemia and the duodenal ulcers were due to an outpouring of adrenalin into the blood stream. The fact that the leukocytes were not increased in number suggests that the polycythemia at least in some of these cases may have been an erythrocytosis rather than a true polycythemia vera. Bing,[1] writing in 1920, again refers to the relationship between polycythemia and duodenal ulcer as observed by Danish workers. In 1 of his own cases the red cells numbered 7,000,000 in

* Read at the meeting of the Association of American Physicians, at Washington, D. C., May 10, 1933.

blood taken from the ear, and 8,200,000 in blood from the skin of the abdomen. He believes that gastric hypersecretion and repeated vomiting, by leading to concentration of the plasma, were the chief causes of the polycythemia, which would therefore be secondary rather than primary in character.

Polycythemia may be associated with gastric rather than duodenal ulcer. Weber and Watson[11] and also Schneider[10] have described such cases. In both of these cases there appears to have been a polycythemia vera with increase in the white cell count and hyperplasia of the bone marrow. In Schneider's case there was a marked degree of myocardial fibrosis (*vide infra*).

The case about to be described was characterized by polycythemia, leukocytosis, splenomegaly, duodenal ulcers, myocardial fibrosis, coronary artery occlusion, and marked ascites. The question whether the increased red cell count should be regarded as a true polycythemia or a secondary erythrocytosis is discussed below.

Case Report.—The patient, a man, aged 37, was admitted to the Winnipeg General Hospital under the care of Dr. Charles Hunter on October 12, 1932, complaining of enlargement of the abdomen and shortness of breath of a few weeks' duration, and of abdominal pain for the past 10 months. This pain, which was located in the epigastrium, was at first vague in character, but gradually became sharp and severe. It did not radiate, and was never accompanied by vomiting until a week before admission, when the patient vomited twice. It was relieved by taking food. The previous history was essentially negative. There was no complaint of dizziness nor other cerebral disturbance.

The chief feature of the clinical examination was the great abdominal distention, most of which was due to the presence of fluid, although the liver and spleen were found to be moderately enlarged. No cardiac abnormality was detected, apart from a soft apical systolic murmur. The electrocardiogram was normal. This is of particular interest in view of the subsequent postmortem findings. The systolic blood pressure was 140, the diastolic 96. A very slight degree of edema was present in both legs. Paracentesis resulted in the withdrawal of 3890 cc. of fluid, which was light yellow in color, with a specific gravity of 1.014, and an albumin content of 1 per cent. During the following 2 months paracentesis was performed on 9 occasions, the amounts withdrawn varying from 3280 cc. to 5400 cc. Urinalysis was negative. Gastric analysis showed normal free HCl and total acids. The stool occasionally showed traces of blood. The icterus index varied from 16.5 to 21, and the serum bilirubin from 2 to 2.9. The van den Bergh test gave a biphasic reaction. The urobilinogen varied from 1 in 10 to 1 in 60 dilution of urine. The bromsulphthalein test for liver function showed 10 per cent retention of the dye.

Repeated blood counts were made. The erythrocytes were always increased in number. The lowest count was 5,200,000, there were several just over 6,000,000, and the highest was 8,000,000. The hemoglobin varied from 90 to 118 per cent. On every occasion there was a well-marked leukocytosis, the lowest being 23,400, and the highest 34,350. The most striking feature of the differential count was the remarkably high percentage of polymorphonuclears, which varied from 89 to 97 per cent. No abnormal white cells were observed. The color of the face was high, particularly in the later stages, but this feature was not sufficiently striking to allow of a diagnosis of polycythemia vera.

During his stay in hospital the patient steadily lost weight. From 176 pounds on admission, his weight fell to 147 pounds shortly before his death which took place 2 months later. The shortness of breath mentioned on admission was not observed during the time that he remained in bed. At no time were the symptoms such as to suggest the possibility of a serious cardiac lesion. With the loss in weight, his general condition grew gradually worse. On December 10 he vomited several ounces of bloody fluid which clotted on standing. The vomiting continued, and he died on December 14.

Postmortem Examination. At the autopsy particular note was made of the high color of the face and upper part of the chest. The abdomen was hugely distended, but there was no edema of the legs. The abdominal distention was due to the presence of 2000 cc. of fluid, but there was no effusion in the pleural and pericardial cavities. The heart, which weighed 325 gm., was moderately dilated. Many large scars traversed the anterior wall of the left ventricle. At the apex of the heart the wall of the ventricle was extremely thin over an area 3.5 cm. in diameter. In this area there was an outward bulging of the cavity of the ventricle, if the expression may be allowed, but no bulging of the wall itself was visible on the outside. The inner surface of the herniation was of a dense white color, and presented yellow plaques and patches of calcification, so that the appearance closely resembled that of an atheromatous patch in the aorta. There was no sign of recent infarction. The valves were normal. At a point 1.5 cm. from the mouth of the left coronary artery, its anterior descending branch was occluded by a firm thrombus which filled the lumen as far as the vessel could be followed. Microscopic examination showed later that the occluding mass in the upper part of the vessel was of a very different character from that which filled the lower part. The part of the artery proximal to the thrombus was not atheromatous, nor was the right coronary. The aorta was also free from atheroma. The lungs merely showed edema.

The stomach and intestines were bright red in color and covered with a fine fibrinous exudate. The stomach was greatly distended, but showed no ulceration. On the anterior wall of the duodenum just beyond the pyloric ring there was a small ulcer 1.5 cm. in diameter. The ulcer was deep, its floor and edges were indurated, and in the base there was a small perforation which was responsible for the general peritonitis. Another chronic ulcer was present on the posterior wall, but this was much larger, measuring 2.8 cm. in diameter. The floor was formed by the head of the pancreas. The liver, weighing 2200 gm., was considerably enlarged. The outer surface was finely granular, and the cut surface showed a marked picture of chronic venous congestion. The portal vein was carefully examined for evidence of thrombosis or phlebitis, but none was found; the vessel was entirely empty of blood.

The spleen weighed 1000 gm. and was very greatly enlarged, but the greater part of its bulk was hidden by the ribs. The capsule was thickened. The organ was friable but quite firm. The cut surface was of a dark red color, and showed no infarcts. The splenic vein was examined for thrombophlebitis, but was found to be normal. The kidneys, adrenals, prostate and bladder were normal. The bone marrow in the long bones (femur, tibia, humerus) was abundant and bright red in color, giving every evidence of hyperplasia. The brain was not examined.

Microscopic Examination. Heart: Sections of the wall of the left ventricle show numerous areas of fibrosis with complete replacement of the myocardium. The apical lesion already described consists of extremely dense fibrous tissue.

Left Coronary Artery. In a section taken 6 cm. from the origin of the vessel the lumen is occupied by a mass of fibrous tissue which blends with a thickened intima. This mass presents 3 small channels which contain

red blood cells, and there are in addition a number of tiny lumina (Fig. 1). It is a typical picture of an organized thrombus which has become recanalized. The new channels are not only lined by endothelium, but each presents a separate internal elastic lamina. Sections of the proximal part of the artery show a uniform fibrous thickening of the intima without any evidence of atheromatous degeneration; in these sections the lumen is occupied by a fresh thrombus. The lungs are markedly congested; the alveoli contain many heart-failure cells. The liver is the seat of an extreme degree of central congestion, with complete disappearance of the liver cells in the affected areas; the peripheral zones are relatively intact. In the kidney the glomeruli are markedly congested and swollen, so as to occupy the entire capsular space. In the subcapsular zone, however, the glomeruli are shrunken, and many of the capsular spaces contain a large amount of plasma. In the pancreas there is practically no congestion; the acini show a patchy mucoid degeneration, and many of the islets, especially in the tail, are strikingly enlarged. In the spleen the lymph follicles are small and few and far between. The pulp is uniformly replaced by a diffuse arrangement of rather large cells, polyhedral or elongated, with vesicular nucleus and abundant cytoplasm. The endothelium lining the sinusoids is markedly swollen, and resembles in character the cells which replace the pulp. The amount of blood in the organ is not increased, nor is there any evidence of undue hemolysis. This is contrary to the opinion of Weber,[11] who considers that the splenomegaly is partially due to hyperplasia of the splenic pulp associated with increased hemolysis, but in agreement with the experience of Minot,[8] who found no postmortem evidence of hemolysis.

The duodenal ulcers present the usual picture of a chronic peptic ulcer (Fig. 2). The ulcerated surface is covered by necrotic material, and the submucosa and muscularis are replaced by dense fibrous tissue. The bone marrow of the long bones is in a condition of extreme hyperplasia. The fat of the yellow marrow is entirely replaced by large numbers of erythrocytes and normoblasts, and myelocytes are even more numerous (Fig. 3). It is a combined erythroblastic and leukoblastic hyperplasia.

Comment. The points which particularly call for discussion are: (1) is this a case of polycythemia vera or merely of secondary erythrocytosis? (2) what is the relation between the blood condition and the coronary thrombosis? (3) what is the relation between the blood condition and the duodenal ulcers? (4) what is the cause of the ascites?

1. The question of determining whether a case is one of polycythemia vera or of secondary erythrocytosis may be one of singular difficulty. Even so great an authority on the subject as Weber confesses his inability to decide the matter in many of the examples which he quotes. For one thing, it is not easy to state with exactness the exact level to which the red cell count must rise before it can be regarded as pathologic, and a count of 6,000,000 or even higher may be physiologic for certain individuals. In such persons, however, the leukocyte count is normal. Secondary erythrocytosis is frequently met with in conditions where there is an increased demand for oxygen, but in the case under consideration there is no indication that such a demand existed. Moreover, in secondary erythrocytosis the leukocytes are not increased in number, nor

FIG. 1.—Organized thrombus in coronary artery. Three new channels containing blood have been formed in the thrombus. × 30.

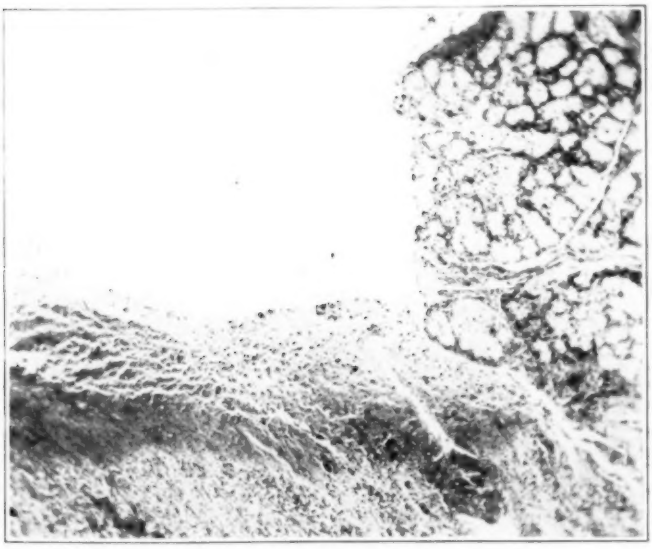

FIG. 2.—Duodenal ulcer. × 40.

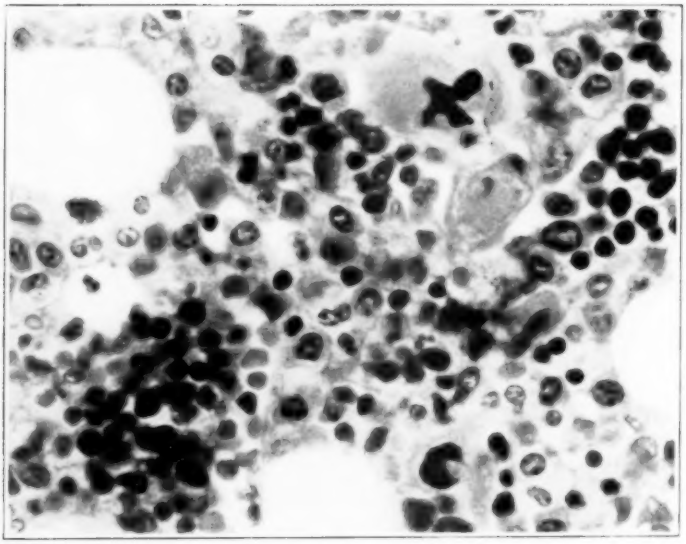

FIG. 3.—Bone marrow of humerus, showing normoblastic and myelocytic hyperplasia. × 600.

does the bone marrow show the myelocytic response which was present in our patient. It may be suggested that the outpouring of fluid into the abdomen led to marked concentration of the blood with a resulting increase in the erythrocyte count, but this would not account for the hyperplastic marrow or the leukocytosis. For these reasons it appears justifiable to regard the case as one of polycythemia vera. Against this diagnosis is the absence of any marked cyanosis and of the cerebral and other symptoms which are characteristic of the condition. It is not unusual, however, as Christian and other writers have pointed out, for the patient to be pale. There may be a marked variation in the color of the skin, depending on such factors as the rate of blood flow and the state of the vessels.

2. It is not difficult to trace a relationship between polycythemia and coronary thrombosis. The literature contains many instances of thrombosis complicating polycythemia. In most of these the cerebral vessels have been involved, often with resulting softening of the brain; but thrombosis of the portal, mesenteric, splenic, renal and pulmonary vessels has been reported. The only record of coronary thrombosis which I have been able to find is Christian's 4th case, in whom there was bilateral thrombosis of the cerebral arteries and coronary artery thrombosis. In this patient the red cell count was 6,900,000, and the hemoglobin 180 per cent. The viscosity of the blood in polycythemia according to Harrop may be increased from 5 to 8 times owing to the great number of red cells, and this no doubt is the explanation of the tendency to thrombosis. In the present case it must be noted that the coronary artery presents evidence of two different thrombotic episodes. There must have been thrombosis of the distal part of the vessel on some former occasion, with organization and recanalization of the clot and production of the fibrotic lesion at the apex. The thrombus formation in the proximal part of the artery must have been a terminal occurrence.

3. The possible relationship between the polycythemia and the occurrence of duodenal ulcers is the most important question to be decided. The possibility that there may be no causal relationship must be admitted; the association may be purely accidental. On the other hand Friedman, Bing and others, as mentioned above, have described a number of cases in which both chronic duodenal ulcers and a markedly increased red cell count were present, so that the association in the present instance is in no way an isolated phenomenon. It is true that in these cases there is reason to believe that the increased cell count represented an erythrocytosis rather than a polycythemia vera, but in the cases of Schneider and of Weber and Watson there can be no question that the blood condition was a true polycythemia. As regards the question of a causal

connection between the two conditions it appears more probable that the tendency to thrombosis has manifested itself not only in the vessels of the heart, but also in those of the first part of the duodenum, producing in both a destructive lesion with necrosis of tissue. In Schneider's case of polycythemia vera there was an association of extensive myocardial fibrosis and gastric ulcer. Indefinite as is our knowledge of the etiology of peptic ulcer, it is generally agreed that the digestive juice acts upon some area of local necrosis or diminished vitality and that such a local lesion may have a vascular origin. For these reasons it is suggested that the relationship between the two phenomena is probably a direct causal one.

4. It must be admitted that the extraordinarily marked and rapidly recurring ascites refuses to fit into the general picture. Thrombosis of the portal vein would explain everything, as in the case of polycythemia described by Chauffard and Troisier, in whom ascites developed 5 months before death, and autopsy revealed chronic thrombophlebitis with complete obstruction of the splenic vein and the gastroepiploic veins. Manges also records a case of ascites associated with a red cell count of 8,000,000 and 35,000 leukocytes, but no autopsy was performed. In Monro and Teacher's case of splenomegalic polycythemia the lumen of the splenic vein was occluded by an old organized thrombus, which had become partially recanalized, in the same way that the coronary artery had been thrombosed and recanalized in the present case. Careful examination in our own case failed to reveal any thrombosis of the portal or mesenteric veins nor any evidence of phlebitis.

Conclusion. The association in a patient of polycythemia, coronary thrombosis and duodenal ulceration has been used as the basis of a discussion of the question as to whether the duodenal ulcers and polycythemia which may occur in the same patient, as described by several writers, are in any way related. The conclusion arrived at is that the polycythemia probably bears a causal relationship to the duodenal ulceration.

REFERENCES.

1. Bing, H. J.: Ugesk. f. Laeger, **82**, 337, 1920. (Brit. Med. J., 1920, **1**, Epitome No. 625).
2. Chauffard, A., and Troisier J.: Bull. et mém Soc. méd. d. hôp. de Paris, **35**, 610, 1913.
3. Christian, H. A.: Am. J. Med. Sci., **154**, 547, 1917.
4. Friedman, G. A.: Med. Rec., **84**, 701, 1913.
5. Friedman, G. A.: Ibid., **85**, 875, 1914.
6. Harrop, G. A.: Medicine, **7**, 291, 1928.
7. Manges, M.: Med. Rec., **79**, 651, 1911.
8. Minot, G. R., and Buckman, T. E.: Am. J. Med. Sci., **166**, 469, 1923.
9. Monro, T. K., and Teacher, J. H.: Lancet, **1**, 1015, 1913.
10. Schneider, N.: Wien. klin. Wchnschr., **20**, 413, 824, 1907.
11. Weber, F. P., and Watson, J. H.: Internat. Clin., **4**, 47, 1905.
12. Weber, F. P.: Polycythemia, Erythrocytosis and Erythræmia (Vaquez-Osler Disease), London, 1921, H. K. Lewis & Co.

INTESTINAL INTUBATION: A PRACTICAL TECHNIQUE.

By T. Grier Miller, M.D.,
ASSISTANT PROFESSOR OF MEDICINE,

AND

W. Osler Abbott, M.D.,
INSTRUCTOR IN MEDICINE; INSTRUCTOR IN PHARMACOLOGY, UNIVERSITY OF PENNSYLVANIA.

(From the Gastro-intestinal Section of the Medical Clinic, University of Pennsylvania Hospital.)

The desirability of intubation of the human small bowel beyond the duodenum for the study of intestinal physiology as well as for diagnostic and therapeutic purposes has been appreciated since the introduction of stomach and duodenal tubes. Isolated descriptions of its accomplishment have appeared from time to time, but none of the methods has proved practical, chiefly because of the time required for passage of the apparatus into the bowel and because the tubes employed have been too small to permit ready extraction of the jejunal or ileal contents. The apparatus which we have developed and the technique for its use which we will describe not only overcome these two objections, allowing ready passage throughout the jejunum, often into the ileum, and supplying an adequate lumen for the extraction of intestinal contents, but also permit simultaneous kymographic records of pressure changes within two areas of the upper half of the digestive tract or the injection of substances directly into the stomach, duodenum or the small bowel itself at any desired point above the termination of the tube. Furthermore, its introduction is little more disturbing to the subject than the passage of an ordinary duodenal tube, and it is easily and quickly removable by the mouth.

Literature. Scheltema,[1] in 1908, gave the first description of successful intestinal intubation, referring to it as permeation or sounding of the gastro-intestinal tract. In animals he was able to pass a small rubber tube through the entire tract, removing it per rectum, and finally accomplished intestinal intubation in a few children, using a tube of 3.8 mm. diameter (No. 11 F.) with a bulbous distal extremity. He referred to its possibilities for the introduction of medicinal substances in cases of intestinal parasites and cholera infantum, but apparently did not consider the aspiration of contents practicable. His tube was introduced by the nose and required several days to reach the small bowel.

In 1919, Einhorn,[2] unaware at the time of Scheltema's experiments, described the use of a soft rubber tube, 8 mm. in circumference (No. 8 F.), with an attached perforated capsule, for the injection of fluids into the intestinal tract. It, also, required much time

to reach the small bowel and was too small to permit aspiration of the contents. Buckstein,[3] in 1920, referred to the use of an intestinal tube for the injection of a barium mixture in order to study loops of the small bowel by the Roentgen ray. He was able to pass his tube 120 to 150 cm. beyond the teeth (60 to 90 cm. beyond the pylorus), and suggested its use for the study of the physiology and bacteriology of the small intestine. Einhorn,[4] during the following year, described a jointed tube of No. 8 F. size, made up of sections of 1 meter length, which he claimed permitted aspiration at 1 and sometimes 2 meter depths, but it was too small for extractions at lower levels. No studies on aspirated specimens were reported. In order to get this tube into the jejunum and ileum, repeated feedings and much time were required. A single case was referred to, the tube reaching the cecum on the 3d day; at that point it was employed for the instillation of medicated fluids as treatment for an ulcerative colitis; it was finally evacuated per rectum. Later, in 1923, he[5] reported its use in 2 other cases of ulcerative colitis: in these it required respectively 7 and 6 days for the tube to reach the cecum; in both the tube was removed by mouth.

Einhorn's jointed tube, while satisfactory for the instillation of fluids, has proved impracticable in our hands because of repeated failures to get it beyond the duodenum and upper jejunum, the time required and its small lumen. No further reports on its use have been discovered and it is not now manufactured.

Apparatus. The apparatus (Fig. 1) which we have finally developed has grown out of a considerable personal experience with various types used for experimental and clinical studies on the duodenum and small bowel. Its special virtues lie (1) in the fact that it has at its distal end a collapsible rubber bag, which, when distended, may be grasped by the peristaltic waves and carried along relatively rapidly in the intestine, and (2) in the fact that the tube has two lumina, one of which is used for inflation and deflation of the rubber bag while the other remains free for extraction and injection purposes.

Before securing a double-lumened rubber tube we experimented with two separate tubes, one within the other, this arrangement giving theoretically all the advantages of the present apparatus, but often the space between the walls of the two tubes, used for aspiration purposes, became occluded; also, the inner tube had too small a lumen to permit satisfactory kymographic records. It served, however, to demonstrate the practicability of our proposition for a double-lumened tube.

Much difficulty was encountered in having a double-lumened tube of sufficient length manufactured. About fifty of the more important producers of medical and special rubber goods in this country were visited or written to, but only one* thought it possible to make such a tube and was willing to undertake some experiments.

* U. S. Rubber Products Company of New York City.

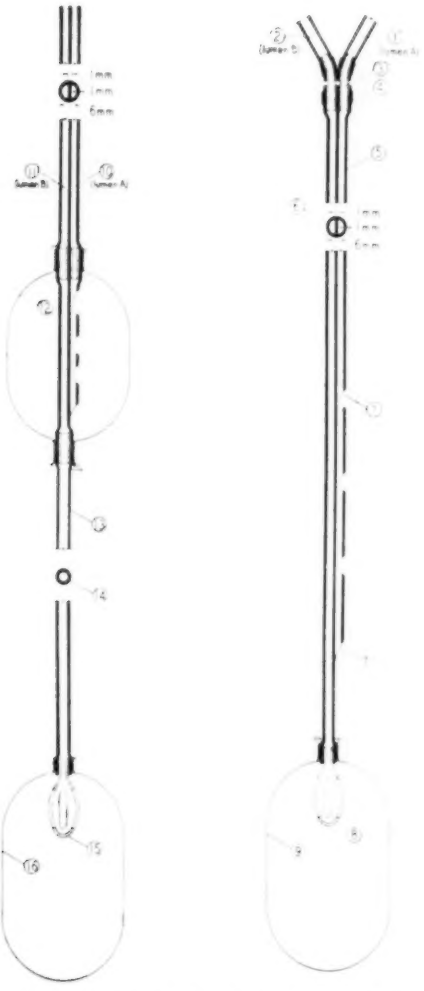

FIG. 1.—Longitudinal sections of double-lumened rubber tube (*right*) and of double-lumened tube with single-lumened tube attached (*left*). In each the lumen on the right side is referred to as "A" and the other lumen as "B." 1, indicates a proximal tube communicating with "A;" 2, one communicating with "B" (different colors); 3 indicates a brass cannula for making the connection between a lumen of double tube and proximal single tube; 4, thread holding two brass tubes in place; 5, outer wall of double-lumened tube; 6, transverse section of tube; 7, opening into lumen "A;" 8, Rehfuss bucket; 9, rubber bag (condom or finger cot); 10, lumen "A;" 11, lumen "B;" 12, rubber bag attached at proximal end over brass cannulæ in two lumina, at distal end over single brass tube in lumen "B;" 13, single tube, connected proximally by means of brass cannula to lumen "B;" 14, cross section of single tube.

FIG. 2.—Roentgenogram showing apparatus in the stomach, duodenum, and upper half of the small intestine. The outer wall of one section of the double tube was cut away from the distal part of the tube, leaving only a single tube (lumen "B") beyond the arrow. Bag at distal end of lumen "B." This apparatus is useful for injecting substances into the bowel well above the distal end and for securing records of pressure changes from the bowel at the distal end of the tube. Lumen "B" and bag filled with 8% sodium iodid solution. (Postero-anterior view.)

That organization was finally able to supply us with the tube illustrated (Fig. 1). It has an outside diameter of 6 mm. (having, therefore, a caliber of No. 18 F.). Its walls and the partition are of 1-mm. thickness: the two lumina are of equal size, each a little larger than that of the ordinary duodenal tube. It is reasonably flexible, does not kink on sharp bending and has a fairly smooth external surface. An ideal tube would be slightly more flexible and have a smoother surface: we are trying to secure such a tube.

The details of the apparatus are given in the illustration and its legend. It is advantageous to have the two proximal rubber tubes (1 and 2 of Fig. 1) of different colors so that it is always obvious with which lumen each is connected. The duodenal or gastric metal capsule at the termination of the tube is not necessary but has seemed to render entrance into the duodenum easier; also, it serves as an end piece about which the bag may be attached.

It will be noted that one of the apparatuses illustrated consists of a double tube to which a single tube is attached. This is a convenient arrangement for obtaining two simultaneous kymographic records, or (when the proximal bag is omitted) for the injection of fluid substances at a distance above the termination of the apparatus. Other modifications will readily suggest themselves, and others have been employed by us.*

Technique. The technique of intubation, as we have practised it, is simple. The tube with the bag deflated is taken by the fasting subject in the early morning, exactly as are gastric and duodenal tubes, only enough being swallowed at first to reach the stomach, and then with the subject reclining on his right side, more is introduced slowly until the distal end has reached the duodenum. Entrance into the duodenum may be determined by the character of the contents obtainable through lumen "B," or preferably by fluoroscopic observation. The special posture is no longer required but a little more tube is taken and fluoroscopic observations are made until the capsule has reached at least the third portion of the duodenum. Then the bag is distended moderately with air or an 8% sodium iodid solution (to render visualization of the tube and bag easier). After this the subject swallows about 5 cm. of tube every 10 min., fluoroscopic observations being made from time to time until the distal end has reached the desired point (Fig. 2).

We have found that within 6 hours the tube has usually passed along the bowel to a distance of 120 to 150 cm. beyond the pylorus. According to Einhorn the length of tubing required to reach from the pylorus to the cecum in the living human is approximately 270 cm.: this suggests that our tube usually reaches the half way point in the small bowel within 6 hours. In confirmation of this is the fact that fluoroscopic observation of a barium solution injected at the termination of a tube passed 120 to 150 cm. beyond the pylorus

* This apparatus or special modifications of it may be secured through Edward P. Dolbey and Company, 3621 Woodland Ave., Philadelphia.

does not usually show evidence of valvulæ conniventes, which are present only in the upper two-fifths of the small bowel, the jejunum; this indicating that the ileum has been reached.

Thus, without the necessity of having the subject take any food and within the early half of the day, the apparatus can be introduced into the upper ileum. Beyond this point it does not go so rapidly, probably because of the slight rigidity of the tube, but we anticipate that with an improved type of tubing even deeper penetration may be secured within the same period of time.

Once in the position desired the apparatus may be used for various purposes: with the bag inflated moderately and lumen "A" connected with a recording apparatus, continuous kymographic records of pressure changes may be secured; if the apparatus is equipped with two bags, simultaneous records from two areas may be obtained; when the bag is deflated, and the other lumen ("B") communicates with the interior of the bowel, aspirations may be made or substances may be injected at a fixed point.

Value of the Technique. It is not our purpose to refer to special studies made with this technique in this communication, but we may say that certain investigations of the chemistry and physiology of the small bowel are under way; also studies on the motor effects upon the bowel of drugs administered orally, by lumen "B" of the tube, and by hypodermic injection. Shiffer,[6] of our Section, using a modification of the apparatus, has perfected a technique for obturation of the lower duodenum and retrograde filling of that organ with an opaque substance which provides a satisfactory method for differentiating by the Roentgen ray certain obscure duodenal lesions. Bacteriologic study of the contents of the small bowel under fasting conditions and after the administration of certain types of food, also investigation of the anatomical relationships of the coils of the jejunum, are planned.

It is believed that this apparatus and the technique described furnish a direct means of studying many problems in the human that could not be attacked satisfactorily before, and it is hoped that other workers will become interested.

Conclusions. 1. A new apparatus, involving the use of a newly developed double-lumened rubber tube, for intubation of the human small intestine, and the technique for its employment are described.

2. By means of a rubber bag, attached at the distal extremity of the tube over an Einhorn or Rehfuss duodenal bulb and distended when it enters the lower part of the duodenum, the apparatus is pulled along the intestinal tract by peristaltic waves.

3. As now developed, the distal part of the apparatus will usually reach the upper ileum within about 6 hours, and it is believed that further developments may lead to even deeper penetration within the bowel.

4. The apparatus may be used to secure intestinal contents from,

or to inject substances into, any area within the upper half of the intestinal tract or to secure records of pressure changes from a fixed point of the tract or simultaneous records from two areas. It may lead eventually to new methods of diagnosing and treating intestinal lesions.

REFERENCES.

1. Scheltema, G.: Arch. Roent. Ray and Allied Phenomena, **13**, 141, 1908–1909.
2. Einhorn, M.: New York Med. J., **110**, 456, 1919.
3. Buckstein, J.: J. Am. Med. Assn., **74**, 664, 1920.
4. Einhorn, M.: Am. J. Med. Sci., **161**, 546, 1921.
5. Einhorn, M.: New York Med. J., **117**, 214, 1923.
6. Shiffer, P. H.: Roentgenographic Examination of the Duodenum After Intubation and Obturation. Presented for degree of Master of Medical Science, Graduate School of Medicine, University of Pennsylvania (to be published).

THE ENDOCRINE EFFECTS OF CERTAIN OVARIAN TUMORS.*

By Emil Novak, M.D.,

Associate in Gynecology, Johns Hopkins Medical School; Visiting Gynecologist, St. Agnes' and Bon Secours Hospitals,
Baltimore, Md.

(From the Gynecological Department of Johns Hopkins Medical School.)

A phase of endocrinology which so far has remained almost untouched, at least in our American literature, is that dealing with the possible hormone effects of certain gonadal tumors, more particularly those of the ovary. This is rather surprising in view of the recognized hormonal influence of certain tumors involving other endocrine structures. To take the most conspicuous example, the adenomata of the pituitary, both those of the acidophilic and basophilic types, are accepted as bearing a causal relation to certain more or less clearly defined syndromes. Adenomata of the suprarenal cortex likewise have in some cases been shown to be responsible for the production of such syndromes as precocious puberty and virilism, and such syndromes have disappeared after removal of the tumors. With reference to the thyroid, such endocrine effects are not so clearly definable in the case of genuine neoplasms, whereas in the case of pineal tumors, a considerable number of reported cases would seem to indicate their capacity to evoke striking endocrine syndromes, involving practically always males, and characterized most often by such evidences of a disturbance of sex characters as premature maturity or hypertrichosis, often with obesity.

Such observations are explainable only on the basis of a persisting and excessive function of the tumor cells, so that even very tiny tumors are capable of evoking profound body changes. This is

* Read before the American Association for the Study of Internal Secretions, Annual Meeting, Milwaukee, June 12, 1933.

strikingly illustrated in Cushing's description[1] of the amazing effects produced by even very small basophilic adenomata of the anterior pituitary lobe. Since the function of the constituent cells is apparently only an exaggeration of the normal function of the basophilic cells of the anterior lobe, it seems almost incredible that such massive total overfunction could emanate from such tiny lesions. Smith suggests as an explanation that under normal conditions the anterior hypophysis functions at a very low level, far below its full capacity, so that even a small mass of highly overfunctioning cells may bring about a violent endocrine upheaval.

As regards the ovary, it has long been known that certain tumors may produce remarkable changes in the individual, along both physical and physiologic lines. These changes are always in the nature of disturbed sex character differentiation, so that, in the consideration of this subject, we are at once thrown into the chaos surrounding the question of sex differentiation in general. Many different types of ovarian tumor have, if one may judge from the literature, been found in association with disturbances of the sex characters. It should be remembered, however, that most of these cases, especially those in the older literature, are incompletely or unauthoritatively reported, so that we are left in ignornace or doubt as to the pathologic diagnosis. Furthermore, in some cases coëxistence of an ovarian tumor with a certain syndrome has led to the unwarranted assumption that the two are causally related, whereas a careful observation of the subsequent course would belie such an assumption.

A crucial test of the etiologic relation of ovarian tumors to endocrine syndromes is afforded by the disappearance or regression of the symptoms after removal of the tumors. This criterion has been applied most successfully in the case of certain ovarian tumors which had been generally unrecognized up to very recent years, and it is with these that this paper chiefly deals. Its object, briefly stated, is to show that certain ovarian tumors possess the capacity of hyperfeminizing the individual, so to speak, while others produce changes which must be interpreted as indicating a defeminization or masculinization of the female patient.

Granulosa-cell Tumors of the Ovary. These tumors are found most often in elderly patients, but may occur during the reproductive era, and occasionally in young children. They are made up of cells whose individual characteristics and arrangement, as well as physiologic function, are similar to those of the normal follicular epithelium. At times a tendency to the formation of actual follicles is noted, while in other instances the pattern is a much more diffuse one, and may be almost sarcomatous in appearance. I shall not here discuss the pathology and the histogenesis of these tumors, as this has been done fully in a paper to be presented before the Section on Pathology and Physiology of the American Medical Association

at the present session.[2] Suffice it to say that these tumors are now generally accepted as arising from granulosa-cell rests, representing follicular epithelium which has not been used up, so to speak, in the formation of the follicular apparatus of the ovary. This epithelium is a source of folliculin, so that it is not surprising that tumors consisting of this tissue have a distinctly feminizing tendency.

When these tumors occur in women well beyond the menopause, as is so often the case, they produce uterine bleeding which may or may not be free, but which characteristically is periodic, so that it presents clinically as an apparent reëstablishment of the menstrual function. Uterine bleeding at this age is always to be looked upon with suspicion, as it most often indicates uterine cancer. Curettage in cases of granulosa-cell carcinoma yields an endometrium which is in no way suspicious of cancer, but which most often exhibits the hyperplasia pattern so characteristic of functional uterine bleeding in patients during the reproductive epoch, especially those approaching the menopause. There is no longer any doubt that this type of bleeding is an endocrinopathy, the immediate ovarian disturbance being a hyperfolliculinism. Corpora lutea are characteristically absent in such ovaries. There is considerable evidence that behind the ovarian disturbance is one involving the anterior pituitary sex hormones, but this question need not be discussed here.

The point to stress is that the clinical symptoms and the uterine changes associated with granulosa-cell tumors of the ovary, even in very old women, are exactly similar to those associated with excessive folliculin production in women of reproductive age. In each case the follicular epithelium plays the important rôle, so that it is easy to understand why these tumors are capable of bringing about such remarkable rejuvenation changes in the pelvic organs.

Even more striking, perhaps, are the effects produced by granulosa-cell tumors when they occur in children below the normal age of puberty. Only 3 such cases have been reported thus far, although to these I can add 3 more. These were reported in a paper read last month before the American Gynecological Society.[3] Children suffering from granulosa-cell tumors of the ovary characteristically develop the syndrome of precocious puberty, including precocious menstruation. The inauguration of the menstrual function is often preceded by a periodic vaginal discharge. Other manifestations are mammary overgrowth, precocious development of both the external genitalia and the uterus, the appearance of axillary, pubic and genital hair, and increased body growth, with a precocious development of the characteristic feminine contour.

Whatever the individual viewpoint may be as to the underlying cause of sex differentiation, and whatever one's views as to the relative importance in the human of the sex cells and the endocrines, there is no division of opinion as to the influence of the latter in the

production of the secondary sex characters, such as mammary development, growth of hair, etc. Here again the increased endocrine activity of the constituent tumor cells clearly explains the clinical syndrome which the tumor evokes. That overproduction of folliculin actually occurs in these cases has been further confirmed by studies of the folliculin content of the blood and urine in 1 or 2 cases, as well as by the effects produced by injecting tumor material into castrated animals.

I have been much interested in one aspect of this subject which, so far as I know, has received no attention in the literature. Certainly, it would seem that the only ovarian hormone concerned in this clinical picture is folliculin, and yet the associated uterine bleeding, in children or in old women, is often clinically indistinguishable from normal menstruation. This bears out the growing opinion that, insofar as the mere periodic bleeding of the menstrual cycle is concerned, folliculin plays the all-important rôle. Fluctuations in the folliculin level explain the whole bleeding process adequately, as investigators are more and more coming to believe, even though progestin plays an essential rôle in other manifestations of human cyclical activity.

What factor, however, brings about the periodic drop in follicular level which is presumably the cause of the uterine bleeding? This question cannot yet be satisfactorily answered, but the importance of the withdrawal of either the ovum or corpus luteum influence, formerly rather generally assumed, is negated by the observations in cases of granulosa-cell tumors of the ovary. Here we have no ova or corpora lutea to deal with, and yet the bleeding may exhibit exactly the same periodicity as that of normal menstruation. We can only speculate as to the reason for this, but the one which suggests itself is that the folliculin factor is automatic and self-regulating, so that an excess of the hormone evokes some mechanism, possibly pituitary, bringing about a discharge of folliculin, with bleeding as a result. This explanation, as applied to normal menstruation, has already been suggested by various investigators, especially by Moore, although the evidence for its correctness is not yet complete.

Arrhenoblastomata. The other group of tumors to which I should like to refer produce effects upon the sex characters along quite opposite lines, in that they tend toward a defeminization and masculinization of the individual. For the recognition of this group, and for a rational explanation of their histogenesis and their pathologic physiology, we are indebted chiefly to the work of Robert Meyer,[4] who has suggested as an appropriate name for this type of masculinizing tumor the designation "arrhenoblastoma." Pathologically these tumors are to be classed as testicular adenomata, most often of the so-called atypical variety. It has long been known that certain tumors, not only of the ovary, but also of the

suprarenal, pituitary and pineal bodies, may be associated with loss of feminine characters and greater or less degrees of virilism. This is especially true of cortical lesions of the suprarenal, and a considerable group of cases of this sort have been reported in the literature. For the reader interested in this subject a good start may be obtained from the classic paper of Bulloch and Sequeira (1905)[5] and that of Glynn (1914).[6]

It is suggestive that many of the reports concerning ovarian tumors found with such syndromes speak of the tumors being of a "peculiar" or "puzzling" or "unusual" type. Various pathologic diagnoses have been made, such as carcinoma, sarcoma, endothelioma, hypernephroma, granulosa-cell carcinoma, etc. A review of these old cases suggests, in the light of our newer knowledge, that the tumors belong in the category of arrhenoblastomata.

A proper understanding of the histogenesis and biologic significance of these tumors, presupposes some familiarity with two still unclarified subjects, viz., the embryology of the ovary and the mechanism of sex differentiation in general. Neither of these can be discussed within the limits of a short paper. With reference to the development of the normal ovary, it would seem that there is a growing tendency against the older descriptions of von Winiwarter, Felix and others and in favor of the newer viewpoint, championed especially by Fischel,[7] that the real "Keimepithel" is not the germinal epithelium of the ovary, and that the latter is not responsible, as had been believed, for the formation of the follicular apparatus, through the formation of invaginating "medullary columns" and "Pflueger tubules."

According to the newer view, which is apparently substantiated by the large material on which Fischel's study is based, the follicular epithelium is formed by the cortical mesenchyme *in loco*, as a result of a direct transformation of some of the mesenchymal elements into epithelial cells. The latter then group themselves around the germ cells, which Fischel believes reach the sex anlage after migrating from the entoderm of the hind gut. The rete ovarii is likewise formed from the mesenchyme, and is the homologue of the rete testis of the male. Cells in this region may remain in an undifferentiated stage, so that it is understandable that tumors arising from them may develop along either male or female lines.

The close contiguity of the suprarenal anlage with that of the gonad, and the fact that both are derived, if the newer view is correct, from Wolffian mesenchyme, makes it easy to understand why cortical tumors of the suprarenal may give rise to a syndrome very similar to that produced by the tumors originating from the rete region of the ovary. This is particularly true if we accept the view, urged especially by Witschi,[8] that the medulla of the gonad is a "determiner" of masculinity in the germ cell, just as the cortex is a "determiner" of femaleness. This view is supported by a wealth of biologic evidence.

What has been said represents in essence the concept of the origin of arrhenoblastomata which has been suggested by Meyer. It is at once obvious that this question cannot be separated from that of intersexuality, and that it will not be entirely clarified until we know more than we now do as to the factors concerned in the differentiation of the sexes. It may be emphasized, however, that these tumors do not characteristically arise in hermaphrodites or pseudohermaphrodites, but in individuals who had been quite normal before the development of the tumors. In this respect they differ from still another type of ovarian tumor which is becoming more generally recognized, the disgerminoma or seminoma. The latter arise most often in very young individuals with defective gonads, and not infrequently in pseudohermaphrodites. The tumor itself has its origin in cells which have apparently lost all capacity for differentiation, so that no sex hormone influence, either male or female, is produced, and hence such tumors have no influence on sex characters. In other words, while they often occur in pseudohermaphrodites, they have no causal relation to bisexuality.

The arrhenoblastoma, on the other hand, often develops in previously normal individuals, and through its hormone influence, brings about a greater or less degree of sex reversal, with often a virtual pseudohermaphroditism. The tumor, arising from the undifferentiated cells of the rete region, develops in a male direction, and may thus overcome the feminizing influence of the ovarian follicular structures. This is a rather bald way of summing up a very abstruse subject, but that such tumors do actually produce this masculinizing effect admits of no doubt. Women with such tumors cease to menstruate, the breasts atrophy and flatten out, and a heavy growth of hair appears on the face, so that daily shaving may be necessary. The hairy growth may involve also the chest, abdomen and extremities. In a considerable number of cases the voice has become deeper and heavier, and the clitoris has not infrequently been markedly hypertrophied, so as to resemble the male organ. The configuration of the patient may lose the normal feminine curves and become lank and angular.

While these cases are rare, they are of exceeding interest from the standpoint of endocrinology, and perhaps even more from a general biologic viewpoint. They at once suggest a similarity with the instances of sex reversal observed in many of the lower animals. The free-martin of Lillie, the masculinization of hens after tuberculous destruction of the left gonad, the experimental reversal of sex in frogs and many other species—all these phenomena, and many others, come to mind in the consideration of the sex changes produced by arrhenoblastomata. Their discussion in this paper would lead us too far afield.

From a pathologic standpoint, these tumors are also of great interest. Their structure is quite variable. In the first place

tumors of well differentiated mature testicular tissue may occur in the ovary, the so-called testicular adenomata originally described by Pick.[9] These, however, most often have no effect on the patient's sex characters, while on the other hand the atypical testicular adenomata are highly potent from an endocrine standpoint. This may seem anomalous, unless we recall that pseudohermaphrodites with feminine external sex characters may possess well-developed testes, and only testes, with no ovarian tissue.

The tumors often present a rather sarcoma-like picture, but even then there is usually noted a tendency to the formation of small cords or strands of cells, while in other parts definite narrow and perhaps zig-zag tubules may be seen. The cells are oval, spindle or polyhedral in shape, and in a few cases larger cells, interpreted as interstitial cells, have been observed. For a fuller description of these tumors from the standpoint of pathology and histogenesis, I must again refer to the forthcoming paper by the present author, in collaboration with Long.

While both the arrhenoblastomata and the granulosa-cell carcinomata are classed as malignant, they are certainly relatively benign, and in the majority of cases, their removal has been followed by complete cure, with regression of the abnormal changes and the restoration of feminine characteristics, including the menstrual function. A striking demonstration of the causal relation of the tumor to the symptoms is found in the case of Kleinhans, described by Wagner,[10] in which regression of the symptoms followed removal of the unilateral tumor, with return of the masculinization later because of a recurrent tumor in the other ovary. In a small proportion of cases, the tumors, including those of the granulosal variety, have run a malignant course, with recurrence of the tumor after operation, and ultimate death of the patient.

As stated in the early part of this paper, somewhat similar influences have been attributed to other types of ovarian tumors than those which have been described. Ovarian carcinoma of one sort or another, sarcoma, cystadenoma, teratoma and other neoplasms have been held responsible for such manifestations of endocrine activity. There is no doubt that in many of these cases, especially those in the older literature, the tumors were really arrhenoblastomata or granulosa-cell tumors, or that one or other of the latter were associated with the larger tumors to which clinical importance was attached. With sarcoma it is easy to believe that there might actually in some cases be an endocrine function of the cells, if the growth has its origin in undifferentiated cells of the mesenchyma which, as we have seen, is probably the mother tissue of both the follicular epithelium and interfollicular connective tissue.

The only other tumor which, in rare cases, has shown evidences of endocrine activity is the so-called struma ovarii, in which, as a result of teratomatous growth, thyroid tissue is found in the ovary.

Moench,[11] Kovács,[12] and Masson and Mueller[13] have reported instances of this tumor in which the thyroid tissue in the ovary was obviously functionally active. In the case of Kovács, for example, the patient presented the clinical picture of Basedow's disease, and the symptoms disappeared after the removal of the ovarian tumor. Moench's case was somewhat similar, as were those of Masson and Mueller. I have personally observed no instance of this type.

Summary. Certain tumors of the ovary, like tumors of other endocrine glands, are capable of highly developed endocrine function. The two most clearly defined types are the granulosa-cell tumors and the so-called arrhenoblastomata, the latter belonging to the group of testicular adenomata, most often of atypical variety. The granulosa-cell tumors exert a feminizing effect, through the production of theelin by the tumor cells, so that in older women, perhaps far beyond the menopause, they produce most often a hyperplasia of the endometrium associated with periodic bleeding (pseudomenstruation), together with increased size of the uterus. In the few cases seen in very young children, they have produced the syndrome of precocious puberty, with precocious menstruation.

The arrhenoblastomata, on the other hand, have a definitely masculinizing tendency, as might be expected from the fact that they apparently have their origin from undifferentiated epithelium in the region of the rete ovarii. Under conditions which are not clear, these cells, capable of development along either male or female lines, may assume definitely masculine tendencies, as in the group of tumors under discussion. The relation of this endocrine cause of partial sex reversal to the general problems of intersexuality, sex differentiation and sex reversal is obvious, although our knowledge on these subjects is still far from complete.

Patients suffering from arrhenoblastoma present in the extreme instances not only such manifestations of defeminization as amenorrhea and breast atrophy, but also such evidences of masculinization as a masculine type of hair distribution, deepening of the voice, and hypertrophy of the clitoris. Removal of the tumor brings about a regression of these symptoms.

REFERENCES.

1. Cushing, H.: Johns Hopkins Hosp. Bull., **50**, 137, 1932.
2. Novak, E., and Long, J. H.: J. Am. Med. Assn., **101**, 1057, 1933.
3. Novak, E.: Am. J. Obst. and Gynec., **26**, 105, 1933.
4. Meyer, R.: Ibid., **22**, 697, 1931.
5. Bulloch, W., and Sequeira, J. H.: Trans. Path. Soc. of London, **56**, 189, 1905.
6. Glynn, E. E.: Quart. J. Med., **5**, 157, 1911–1912.
7. Fischel, A.: Ztschr. f. Anat. u. Entwickl., **92**, 34, 1930.
8. Witschi, F.: Sex and Internal Secretions, Chapter V, Williams and Wilkins Company, Baltimore, 1932.
9. Pick, L.: Berl. klin. Wchnschr., **17**, 502, 1905.
10. Wagner, G. A.: Zeitschr. f. Geb. u. Gynäk., **98**, 131, 1930.
11. Moench, G. L.: Surg., Gynec. and Obst., **49**, 150, 1929.
12. Kovács, F.: Arch. f. Gynäk., **122**, 766, 1924.
13. Masson, J. C., and Mueller, S. C.: Surg., Gynec. and Obst., **56**, 931, 1933.

A STUDY OF ANHYDREMIA IN DIABETIC COMA.*

By Elaine P. Ralli, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY; ASSOCIATE VISITING PHYSICIAN, THE THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION, BELLEVUE HOSPITAL,

AND

Alice M. Waterhouse, M.D.,

ASSISTANT IN MEDICINE, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK UNIVERSITY; CLINICAL ASSISTANT VISITING PHYSICIAN, THE THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION, BELLEVUE HOSPITAL.

With the Technical Assistance of

Onna Rheinhart,

NEW YORK, N. Y.

(From the Department of Medicine, New York University, and the Third (New York University) Medical Division, Bellevue Hospital.)

The profound dehydration of the patient in diabetic coma results in two serious complications: anhydremia and anuria. Many observers have reported anuria as a frequent and fatal complication.[1,2,3,4,5,6] Peters and his coworkers[7,8,9,10] have studied the serum proteins in diabetic acidosis and conclude that their initial high level is due to blood concentration. Chang and Harrop[11] found the circulating blood volume reduced. One has only to refer to Marriot's[12] review of anhydremia to realize its effect, uncomplicated by ketosis, on the circulation and the ability of the kidney to excrete urine. He points out that after a period of dehydration the administration of water causes an immediate dilution of the blood and an abrupt fall in the concentration of hemoglobin. The blood concentration then gradually increases, the excess of water being in part excreted by the urine and in part taken up by the desiccated tissues. Ultimately if water continues to be administered a condition of equilibrium is attained between the tissues and blood, after which the concentration of the blood remains constant. In addition when anhydremia is present the secretion of urine is greatly decreased, the colloidal osmotic pressure, according to Starling,[13] approaching the arterial pressure in the renal arterioles. Albumin and casts are regularly present in the urine in conditions of anhydremia, suggesting an irritative disturbance of the kidney. In the patient in diabetic coma there are present not only the effects of anhydremia but the additional burden of ketosis. Not, however, until dehydration and anhydremia occur, does the complication of anuria occur. The patient going into diabetic coma excretes large amounts of urine, and as he almost always approaches

* Expenses of this investigation were defrayed by a grant from the Josiah Macy, Jr., Foundation.

the condition of coma slowly, there results from the excessive loss of water extreme dehydration and desiccation of the blood. The effect of this loss of water on the electrolyte balance has been reported in a recent study on 2 diabetic patients by Atchley and his coworkers.[14] Insulin was withdrawn and the patients allowed to develop a severe degree of ketosis. During this period there was a rapid loss of sodium and potassium. The continuance of such a loss would result in a depletion of base in the body enough to cause dehydration of the tissues and a decrease in blood volume.

We are reporting 8 cases of diabetic coma in which a study was made of the blood concentration and the effect of treatment on this concentration.

Procedure. The patients were admitted to the wards of the Third (New York University) Medical Division of Bellevue Hospital. On admission each patient was given an enema of 1000 cc. of physiological saline solution and the return fluid was measured. A gastric lavage of 1000 cc. of saline was also given and the return measured. A sample of blood was taken immediately under oil, and without a tourniquet to avoid stasis. The patient was then catheterized and treatment was begun. This consisted of infusions of saline, to each 1000 cc. of which 50 gm. of glucose was added, and insulin intramuscularly every half hour. The initial dose was usually 40 units and the subsequent doses varied from 25 to 20 units.

The blood was analyzed as follows: the CO_2-combining power of the plasma was done according to the method of van Slyke and Cullen;[15] blood sugars by the Folin-Wu method;[16] non-protein nitrogen by the Folin-Wu method;[17] hemoglobin determinations were done by the Newcomer method[18] and were read in a Klett colorimeter. The hematocrit[19] readings was made in sedimentation tubes. The readings give the volume of cells in per cent. The total solid content of the blood was done on whole blood and in some of the cases on plasma as well. The procedure for this was as follows: the blood having been drawn under oil was placed in bottles containing a weighed and constant amount of oxalate. One cubic centimeter of blood was drawn up into standardized 1-cc. volumetric Ostwald-van Slyke pipettes and run into a weighing dish. This was immediately weighed and the blood then dried in an oven at 80° C. until a constant weight was reached. The dried weight was divided by the weight of the volume of blood used and the solid content of the blood reported in per cent. All total solid determinations, hematocrit readings and CO_2-determinations were done in duplicate.

Results. Table 1 summarizes the results obtained. Four of the 8 cases died. Autopsies were performed on 3 of these. In Case 6, aged 51, postmortem examination showed in the lungs hypostatic congestion and edema. There was a chronic adhesive pleuritis of the right lower lobe and an interlobar plastic pleuritis. The heart showed myocardial fibrosis, arteriosclerosis of the mitral and aortic

valves and a mild degree of coronary sclerosis. There was slight dilatation of the ascending aorta and mild atherosclerosis. The liver weighed 1520 gm. It was hyperemic, microscopically there was cloudy swelling and evidences of chronic passive congestion. The spleen was hyperemic. There was chronic passive congestion of the pancreas and sclerosis of the vessels. The interstitial fibrous tissue was increased and the islands of Langerhans were atrophic. The kidneys showed nephrosclerosis of the arterial and arteriolar type. In Case 8, aged 59, postmortem examination showed a lobular pneumonia of the left lung and pleural edema of the right side. There was bilateral adhesive pleuritis and generalized congestion and edema. In the heart the ventricular endocardium was fibrotic and there was chronic valvulitis of the mitral valve. The liver weighed 2675 gm. There was enlargement with marked fatty changes. Microscopically there was practically no normal liver tissue, the section seemed to consist of fat with atrophic degenerated liver cords. The pancreas showed interstitial fibrosis and fat replacement. The kidneys were normal. In Case 11, aged 55, postmortem examination showed congestion and edema of the lungs. There was arteriosclerosis of the mitral and aortic valves and sclerosis of the coronary vessels. There was diffuse atherosclerosis of the aorta with a moderate degree of calcification. The spleen was soft and there was follicular hyperplasia. The liver and the diaphragm.

TABLE 1.—SUMMARY OF TREATMENT WITH FLUID INTAKE AND URINE OUTPUT DURING THE PERIOD OF KETOSIS.

Case No.	4.	6.	7.	8.	9.	10.	11.	12.
Name	A. B.	H. S.	J. B.	M. O'S.	E. O'C.	M. B.	M. B.	J. K.
Age	16	51	42	59	65	16	55	22
Duration of diabetes	10 yrs.	8 yrs.	Unk.	Unk.	3 mos.	9 mos.	1 yr.	9 yrs.
Duration of present symptoms	12 hrs.	24 hrs.	?	3 days	2 hrs.	2 wks.	2 wks.	18 hrs.
Complications	None	None	Vincent's angina	None	Chr. Tbc.	None	None	None
Hours before acetone free	10½	12½	7	13	13	11½	15½	10
Insulin units	360	390	190	290	220	215	180	350
Carbohydrate (grams)	285	300	150	325	385	310	210	338
Fluid intake (cc.) in period when pt. became acetone free	7030	8400	4975	8500	5040	9270	9025	8850
(*a*) Per cent as infusion	29.1	35.7	21.1	47.1	29.7	32.4	11.0	20.3
(*b*) Per cent as clysis	28.5	47.8	30.2	23.5	0	21.6	22.2	22.6
(*c*) Per cent by mouth and rectum	32.4	16.5	48.7	29.4	70.3	46.0	66.8	57.1
Urine output (cc.)	1640	759	888	1277	3140	6100	2068	2590
Outcome	Good	Death	Good	Death	Death	Good	Death	Good
Ratio of urine output to fluid intake	1:4.2	1:11	1:5.6	1:6.9	1:1.5	1:4.3	1:4.3	1:3.4

There was fatty degeneration and microscopically there was practically no normal parenchyma seen. In the pancreas there were very few islands of Langerhans remaining and those present were hyalinized. Throughout the parenchyma there were numerous strands of fibrous tissue. The kidneys showed a bilateral pyelonephritis with abscess formation in the right kidney. All of the patients who died were over 50 years of age and 3 had been ill for

24 hours or more before admission to the hospital. The previous duration of the symptoms of coma have a very important effect on the outcome of the case. The patient whose symptoms were of shorter duration was complicated by a chronic tuberculosis. All of the patients who died were acetone free at the time of death.

Table 4 summarizes the blood findings before and after treatment in the 8 cases. Tables 2 and 3 show the results in detail on Cases 10 and 11, 1 of which (Case 11) died. In 5 cases the total solid content of the blood indicated blood concentration. Of the 3 cases in which the total solids were not high, Case 9 was definitely anemic. In Case 6 enough blood could not be obtained for analysis until the patient had received fluids intravenously so that the first reading reported is after treatment. In Case 7 the patient was not actually in coma, although there was no doubt that he was rapidly approaching that state.

TABLE 2.—DATA IN CASE 11. M. BR., 55 YEARS. FEMALE; CONDITION ON ADMISSION: COMATOSE.

	Findings on admission	Period elapsed from time of admission			
		1¼ hrs.	5¼ hrs.	10 hrs.	15½ hrs.
Blood:					
Total solids, per cent	28.75	26.3	20.75	20.7	20.45
Hemoglobin, per cent	...	78.8	80.0	88.2	75.2
Hematocrit cell vol. per cent	38.0	36.5	41.5	41.0	36.0
Blood sugar mg.	512.0	512.0	444.0	425.0	235.0
Blood NPN mg.	75.0	46.0	41.0	43.0	35.0
CO_2 vol. per cent	5.0	8.0	27.0	31.0	33.0
Blood pressure	120/70	110/65	.....	156/55	120/65
Urine:					
Vol. (cc.)	240	255	900	233	680
Sugar (gm.)	4.0	12.0	Pres.	7	22
Acetone	4+	4+	3+ to 1+	1+ to 4+	1+
Diacetic	4+	4+	0	1+	0
Albumin	2+	2+	0		
Fluid intake (total)		2000	2795	1000	3230
Amount given by:					
Infusion		1000			
Clysis		.....	.....	.....	2000
Mouth		1000	2795	1000	1230
Insulin units		80	100	40	35
Carbohydrate (gm.)		90	120	30	40

Fluid intake until acetone free, 9025 cc.
Urine output until acetone free, 2068 cc.
Time until acetone free, 15½ hours.

He was dehydrated but, although the fluid content of the blood was decreased, anhydremia was not marked. In other cases a drop in total solids occurred which ranged from 8.3 per cent to 2.4 per cent. This corroborates the findings of Peters[9] and Atchley[14] that dehydration causes a severe anhydremia in patients in diabetic

coma. One realizes also that blood sugar or nitrogen determinations in such concentrated bloods are not true estimates. Since they are reported in milligrams per cent, a reduction of the fluid content increases the relative concentration. In Case 11 the non-protein nitrogen of the blood fell 40 mg. during the period when the total solid fell 8.3 per cent. Peters[9] also found that the non-protein nitrogen fell as diuresis was established. In Cases 6 and 8 in our series, the high non-protein nitrogen persisted in spite of blood dilution and in neither of these cases could diuresis be established.

TABLE 3.—DATA IN CASE 10. M. B., 17 YEARS, MALE; CONDITION ON ADMISSION: COMATOSE.

	Findings on admission	Period elapsed from time of admission				
		3 hrs.	6 hrs.	11 hrs.	17 hrs.	Next day.
Blood:						
Total solids, per cent	24.4	20.9	21.55	22.3	24.5	21.4
Hemoglobin, per cent	111.0	89.4	99.0	....	97.0	94.0
Hematocrit cell vol. per cent	50.0	40.0	42.0	39.0	40.0	37.0
Blood sugar mg.	246.0	444.0	435.0	345.0	333.0	345.0
Blood NPN mg.	....	44.0	20.0	20.0	20.0	20.0
CO_2 vol. per cent	13.0	17.0	19.0	....	30.0	58.0
Blood pressure	150/90	150/85	135/80	144/102	122/80	118/66
Urine:						
Vol. (cc.)	210	1530	2790	1780	1585	2020
Sugar (gm.)	2.0	21.7	69.5	50.2	34.7	38.0
Acetone	4+	4+	2+	1+	Tr.	0
Diacetic	4+	2+	0	0	0	0
Albumin	4+	4+	3+	3+	3+	0
Fluid intake (total)	....	2500	4250	2520	1230	
Amount given by:						
Infusion	....	2000	1000			
Clysis	....	....	2000			
Mouth	....	500	1250	2520	1230	
Insulin units	....	120	40	55	20	
Carbohydrate (gm.)	....	130	110	70	70	

Total fluid intake until acetone free, 9270 cc.
Total urine output until acetone free, 6100 cc.
Time until acetone free, 11½ hours.

In 3 of the 4 fatal cases the diastolic blood pressure was persistently low and in all 4 the systolic pressure was low for the age of the patients, never reaching more than 120 mm. This is an important factor in increasing the tendency to anuria. If the blood pressure cannot be raised to a normal level for the individual and kept at this level, the prognosis is poor, and even if the blood is diluted the urine output remains low. Several observers[5, 6, 9] have found transfusion useful in raising the blood pressure in such cases. The course of the blood pressure is an indication of the progress of the case.

The relation between urine volume and blood dilution is shown in the individual charts of the patients. In the 4 cases that recovered an increased urine output accompanied the diluting of the blood fol-

lowing the intravenous administration of saline. When the dilution was not accompanied by any rise in blood pressure, as in Cases 6 and 8, the urine output remained low and continued administration of fluids was ineffective in increasing it. The total solid concentration of the blood did not always remain low after its initial drop. In Cases 4, 8 and 10 there was a rise above the initial concentration, but in all cases it dropped again. This rise in total solids was not accompanied by an increase in the percent of hemoglobin but was reflected to a moderate degree in the hematocrit readings. In Case 4 the increased blood concentration was directly proportional to a drop in fluid intake. During the first $1\frac{3}{4}$ hours the patient received 1410 cc. of fluid, 1000 cc. in an infusion. Following this the total solids fell 0.55 per cent. In the next $1\frac{3}{4}$ hours the patient received no infusion and only 210 cc. of fluid by mouth and the total solids rose 1.6 per cent. Again an infusion was given and the total solids fell 1.1 per cent. The urine output reflected the blood concentration. In Case 8 the blood concentration rose in spite of continued administration of fluids, only to drop again to a level lower than on admission in the next 3 hours. In Case 10 after an initial drop of 3.5 per cent the total solids rose slowly and after 17 hours were the same as on admission. This again was apparently a reflection of the amount of fluid administered and also perhaps of the route used. When infusions were given the fall was abrupt and remained lower. When the fluids were given by mouth and the amount was reduced, a gradual rise occurred. The urine output in this case was always good. Cases 9 and 11 both had a good urine volume following blood dilution, and in both there was a temporary rise in blood pressure. Peters[9] noted a tendency for the serum to remain concentrated throughout the first periods of treatment, in spite of administering large amounts of fluid, and to become diluted later even when small amounts were given. Case 9 died suddenly, apparently of circulatory collapse. Whether the low blood sugar of 54 mg. was a factor in bringing this about, it is impossible to say.

In all 8 cases there is a marked difference between the fluid intake and the urine output. The latter only represents a part of the fluid output of the body and we did not attempt to estimate the water put out through the lungs or the skin. The differences, however, are so great that one can gain a fair idea of the degree of dehydration by the amount of fluid retained. In Case 7, where it was possible to weigh the patient, in $17\frac{1}{2}$ hours there was a gain of $7\frac{1}{4}$ pounds. In Table 1 we have shown the ratio of fluid intake to urine output during the period of time that the urine became acetone-free. In Cases 9 and 10 the differences are not as marked as in the other cases, in which at least three times as much fluid was given as was put out in the urine. In Cases 6 and 8, both of whom died, the difference was marked. These were the cases with persistently low blood pressures.

TABLE 4.—BLOOD FINDINGS ON ADMISSION AND AFTER TREATMENT.

No. Case	Age.	Total solids %		Hemoglobin %		Hematocrit.		Blood sugar mg.		NPN mg.		CO_2 vol. %		Blood pressure.		Result.
		On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	On admission.	After treatment.	
4	17	22.25	19.85	94.7	72.3	46.5	37	500	99	42	30	17	50	128/75	118/84	Improved.
6*	51	21.65*	19.35	84.0	74.6	75.0	37.0	476	500	67	57	8		70/48	76/58	Died.
7	42	21.35	20.1	....	87	42	36	212	200	36	36	41	51	110/80	110/75	Improved.
8	59	23.4	20.9	121	94	54	46	454	417	86	75	20	24	98/64	120/64	Died.
9	65	17.3	17.4	73.5	69.4	34	34	270	54	22	17	32	55	122/58	110/50	Died.
10	17	24.4	21.4	111	94	50	37	246	345	..	20	13	58	150/90	118/66	Improved.
11	55	28.75	20.45	....	75.2	38	36	512	235	75	35	5	33	120/70	120/65	Died.
12	22	25.0	22.0	....	94.7	42	47.5	444	113	32	20	13	33	144/90	112/80	Recovered.

* Taken after 3000 cc. of fluid had been given.

Discussion. There seems to be little doubt that blood concentration is present in patients in diabetic coma. In discussing the nature of diabetic acidosis, Peters[10] stresses the importance of blood concentration, shock and the low blood pressure in producing the symptoms. Alkali deficits of the degree found in diabetic acidosis may be produced experimentally or may occur in other diseases without causing the clinical state encountered in diabetic coma. We have already pointed out that until dehydration and anhydremia supervene, the patient is not comatose. That this state of dehydration is the result of the extreme diuresis which accompanies the glycosuria resulting from the uncontrolled diabetic state is shown in the 2 patients studied by Atchley and his coworkers.[14] During the period of insulin withdrawal the water content of the blood fell gradually so that at the end of the ketosis period it had dropped 1.4 per cent in 1 case and 0.5 per cent in the second. During this time in each case the positive water balance became negative. The total solid concentration in 5 of our cases shows how far this loss of fluid from the blood can progress.

Observations such as these accent the importance of treating the diabetic patient in coma, not only for the existing ketosis, but also for the profound dehydration and the loss of fixed base that has occurred as a result of the diuresis. Insulin will correct the disturbed carbohydrate metabolism. It will render available that base from which bicarbonate has been displaced by ketones within the body,[10] but it cannot replace the available base that has already been excreted in the urine.

We have found no difficulty in giving large amounts of saline infusions, provided the blood pressure can be maintained. The patient in Case 10 in the present series is an uncoöperative patient, who stops taking his insulin at intervals. He has been admitted four times in coma since the admission reported here. On each occasion he has received from 4000 to 6000 cc. of saline by vein. When infusions fail to raise the blood pressure, transfusions should be tried.

Summary. Eight cases of diabetic coma are reported. Of these, 5 showed extreme desiccation of the blood as measured by the total solid concentration.

Following infusions and fluid the total solid concentration fell.

Of the 8 cases, 4 died. In these 4 the blood pressure, especially the diastolic, remained persistently low. All of the patients who died apparently had circulatory collapse. Autopsies were done in 3 cases. One had myocardial fibrosis and coronary sclerosis, 1 fibrosis of the ventricular endocardium and the third, sclerosis of the coronary arteries, any of which may have contributed to the circulatory failure.

The fluid intake during the period of ketosis exceeded the urine output.

The importance of fluids in treatment of diabetic coma is stressed.

BIBLIOGRAPHY.

1. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.
2. Imrie, C. G., and Skinner, E. F.: Lancet, **1**, 14, 1924.
3. John, H. J.: J. Am. Med. Assn., **93**, 425, 1929.
4. Begg, A. C.: Lancet, **2**, 69, 1925.
5. Coburn, A. F.: Am. J. Med. Sci., **180**, 178, 1930.
6. Lawrence, R. D.: Brit. Med. J., **1**, 677, 1930.
7. Peters, J., Bulger, H., and Eisenman, A.: J. Clin. Invest., **1**, 451, 1924.
8. Bulger, H. A., Peters, J. P., Lee, C., and Murphy, C. F.: Arch. Int. Med., **36**, 857, 1925.
9. Peters, J. P., Kydd, D. M., and Eisenman, A. J.: J. Clin. Invest., **12**, 355, 1933.
10. Peters, J. P., Kydd, D. M., Eisenman, A. J., and Hald, P. M.: Ibid., p. 377.
11. Chang, H. C., Harrop, G. A., Jr., and Schaub, B. M.: Ibid., **5**, 407, 1927–1928.
12. Marriot, W. M.: Physiol. Rev., **3**, 275, 1923.
13. Starling, E. H.: J. Physiol., **24**, 317, 1899.
14. Atchley, D. W., Loeb, R. F., Richards, D. W., Jr., Benedict, E. M., and Driscoll, M. E.: J. Clin. Invest., **12**, 297, 1933.
15. Van Slyke, D., and Cullen, G. E.: J. Biol. Chem., **30**, 289, 1917.
16. Folin, O., and Wu, H.: Ibid., **41**, 367, 1920.
17. Folin, O., and Wu, H.: Ibid., **38**, 81, 1919.
18. Newcomer, H. S.: Ibid., **37**, 465, 1919.
19. Wintrobe, M. M.: J. Lab. and Clin. Med., **15**, 287, 1929.

AUTOGENOUS VACCINES IN RHEUMATOID ARTHRITIS. A CLINICAL STUDY AND CRITIQUE.*

By Charles L. Short, M.D.,

Assistant in Medicine, Massachusetts General Hospital, Research Fellow in Medicine and Assistant in Pharmacology, Harvard Medical School,

L. Dienes, M.D.,

Bacteriologist, Massachusetts General Hospital and Assistant in Bacteriology and Immunology, Harvard Medical School,

and

Walter Bauer, M.D.,

Associate Physician, Massachusetts General Hospital, Tutor and Assistant Professor of Medicine, Harvard Medical School,

Boston, Mass.

(From the Medical Clinic and the Department of Pathology and Bacteriology of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School.)

Freiberg,[1] Klinge[2,3] and others[4,5] have demonstrated that arthritic changes ensue if an antigen is injected into a previously sensitized animal's knee joint. They have interpreted these changes as evidence of an allergic arthritis. Later Freiberg and Dorst[6] presented data which they considered proof that certain cases of rheumatoid arthritis were allergic in nature. They described the method employed in isolating and identifying the organism which

* This is publication No. 13 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School, Boston, Massachusetts.

represented the offending antigen as well as the manner of preparation and administration of the desensitizing vaccine. Their method is therefore briefly summarized. It consists in making cultures from postnasal secretions, infected sinuses, teeth, tonsils and feces. All the organisms obtained on various types of media and under differing gas tensions are isolated in pure culture, heat killed and intradermal skin tests made with each strain. Individual sensitivity to an organism is shown by marked redness, induration and local heat appearing 24 to 36 hours after injection. In other words, the presence of a positive skin test postulates that the offending organism, to which the patient is sensitive, has been isolated. Therapeutic success now depends only on desensitization with minute doses of such organisms. The importance of such work, if established, is obvious, because it not only adds considerably to our understanding of the etiology of rheumatoid arthritis but also puts vaccine therapy in the treatment of this disease on a simple, workable basis.

The study which we wish to present in this paper has been carried out in an attempt to evaluate critically the soundness of this method of determining a patient's susceptibility to autogenous organisms. We realize the difficulty in the interpretation of therapeutic results obtained over a comparatively short period of time in conditions like chronic arthritis. We have therefore restricted ourselves to making intradermal tests with organisms isolated from foci of infection as well as from the upper respiratory tract and feces in a series of patients with rheumatoid (atrophic) arthritis. However, in order to avoid misleading and fallacious interpretation of the results obtained, we controlled each intradermal test by making similar tests with each strain on three other subjects.

Before reporting our results, we should like to discuss briefly the value of some of the methods used in determining the specificity of vaccines in rheumatoid arthritis. The methods employed are based on the assumption that rheumatoid arthritis is a disease caused by various bacteria of low-grade virulence. This assumption is entirely hypothetical and the best evidence which supports it, the cultivation of streptococci from the blood and synovial fluid of arthritic patients by certain authors,[7,8] is contradicted overwhelmingly by negative results of others.[9,10,11]

To prepare vaccines which are believed to be specific, with the implication that the strains thus isolated from foci of infection and from the throat, stools, etc., are responsible for the disease, the following methods are used: (1) Complement fixation with the patient's serum;[12,13] (2) the growth-preventing effect of the patient's blood on the strains;[14] (3) the specific sensitiveness of the patient's skin to the vaccines prepared from the different strains.[6]

If these methods gave clear cut and consistent results, they would furnish valuable information concerning the etiological agent. The results previously published are far from doing so and offer

no evidence for the usefulness of these methods in the preparation of vaccines. In order to place dependence upon any one of the above-mentioned methods, one must have the assurance that they are reliable when applied to diseases caused by known bacteriologic agents. Observations of this sort have never been reported. The application, therefore, of such methods to diseases of unknown etiology is not valid. It is highly probable that random examination of a large number of different strains, isolated from various sites in the body by the recommended methods, would not permit us to find with any regularity the correct organism in such diseases as diphtheria, tuberculosis, the typhoid group of infections, chronic gonorrheal infections, etc. In diphtheria, for example, even if we should hit on the right strain, a heated suspension of the bacteria would probably give no complement fixation, and, since the diphtheria toxin is destroyed by heat, no specific skin test. In typhoid fever and paratyphoid infections, the specific bacteria are present only in small numbers in the majority of stools. Therefore, even if one examined 10 to 20 strains selected at random, he could expect to identify very rarely the causative organism either with the complement-fixation reaction or with skin tests. Without special methods, it is impossible to cultivate from a sputum tubercle bacilli which, after cultivation, would give specific skin tests. In chronic infectious diseases the difficulties are greater than in acute processes. If we suppose that rheumatoid arthritis is induced by a certain bowel or throat strain, there is no reason to expect to find the same strain several years afterward in the same location or in infectious foci of later origin.

When we come to examine the application of the different methods in practice, we must say that they are usually applied without the necessary controls and give no information as to the significance of the bacterial strain isolated. Shuster[13] often obtains varying results in the complement fixation with the same strain and believes at least 3 consecutive positive examinations are necessary to determine their specificity. Knowing the difficulties which have been encountered in tuberculosis and gonorrhea with the complement-fixation test, and that no generally accepted opinion exists concerning its value, we believe that no significance should be attributed to a varying test when applied to a strain of unknown etiologic significance.

The theoretical foundations of the growth-preventing effect of the blood for the selection of bacterial strains seem equally insecure. There are no observations published which show that the specific bacterial agent in chronic infections grows better in the patient's blood than in other human blood samples. On the contrary, in the majority of chronic infections a marked resistance develops against the invading bacterium and we should expect an increase rather than a decrease of the bactericidal effect of the blood.

TABLE 1.—RESULTS OF SKIN TESTS WITH VACCINES IN ARTHRITICS AND CONTROLS.

Case number.	Vaccine number.	Strain.	Source.	Diameter of reaction in mm. at 24 hours in: Patient.	Controls. 1	2	3
1	1	Unidentified	Throat	2	0	0	2
1	2	Unidentified	Stool	10	0	2	7
1	3	B. coli	Stool	20	0	0	14
1	4	Strep. non-hem.	Stool	2	0	3	3
2	5	Pneumococcus	Throat	0	10	0	3
2	6	Strep. non-hem.	Throat	0	11	0	3
2	7	Strep. non-hem.	Throat	0	0	10	0
2	8	B. coli	Stool	0	12	30	3
2	9	Strep. non-hem.	Stool	0	10	0	3
3	10	B. coli	Stool	10	4	8	5
3	11	Staphylococcus	Stool	0	10	0	5
3	12	Strep. non-hem.	Stool	0	0	0	0
4	13	Strep. non-hem.	Throat	7	0	0	8
4	14	Strep. non-hem.	Throat	17	6	6	8
5	15	Strep. non-hem.	Throat	0	0	0	7
5	16	Strep. non-hem.	Throat	6	12	0	5
5	17	Strep. non-hem.	Tonsil	3	5	3	6
5	18	Strep. non-hem.	Tonsil	3	5	3	6
6	19	Strep. non-hem.	Stool	15	17	15	27
6	20	B. coli	Stool	35	47	37	52
6	21	Strep. non-hem.	Throat	5	10	20	12
7	22	B. coli	Stool	20	15	6	25
7	23	Strep. non-hem.	Throat	3	10	0	0
8	24	Strep. non-hem.	Throat	3	0	4	4
8	25	Strep. non-hem.	Throat	0	0	0	10
9	26	Strep. non-hem.	Tooth	0	12	4	0
9	27	Strep. non-hem.	Tooth	0	12	0	0
10	28	B. coli	Stool	7	4	7	8
11	29	Staphylococcus	Stool	0	0	0	0
11	30	Strep. non-hem.	Throat	0	0	7	5
11	31	Strep. non-hem.	Throat	0	0	8	6
12	32	Strep. non-hem.	Throat	3	0	3	0
12	33	Strep. non-hem.	Throat	3	0	0	0
13	34	Strep. non-hem.	Throat	0	0	4	5
14	35	B. coli	Stool	22	37	15	0
14	36	Strep. hem.	Throat	0	7	0	0
14	37	Strep. non-hem.	Throat	22	32	10	5
15	38	Strep. non-hem.	Throat	0	5	0	3
16	39	B. coli	Stool	25	30	8	20
16	40	Strep. non-hem.	Stool	10	4	10	8
17	41	B. coli	Stool	20	5	20	3
17	42	Strep. non-hem.	Throat	30	5	0	30
18	43	B. coli	Stool	0	0	5	3
18	44	Strep. non-hem.	Throat	0	0	3	0
19	45	B. coli	Stool	0	0	0	27
19	46	Strep. non-hem.	Tooth	5	0	0	11
20	47	B. coli	Stool	19	15	0	21
20	48	Strep. non-hem.	Stool.	0	0	10	0
20	49	Strep. non-hem.	Stool	0	12	20	5
20	50	M. catarrhalis	Throat	32	25	27	28
20	51	Strep. non-hem.	Throat	0	8	21	0
20	52	Strep. non-hem.	Throat	0	10	0	11
20	53	Strep. non-hem.	Tooth	0	0	0	5
20	54	Strep. non-hem.	Tooth	0	0	0	4
21	55	Strep. hem.	Throat	5	5	19	10
21	56	Strep. non-hem.	Throat	5	5	0	5
21	57	B. coli	Stool	5	5	11	26
21	58	Strep. non-hem.	Stool	0	5	10	20

TABLE I.—RESULTS OF SKIN TESTS WITH VACCINES IN ARTHRITICS AND CONTROLS.—(*Continued.*)

Case number.	Vaccine number.	Strain.	Source.	Diameter of reaction in mm. at 24 hours in: Patient.	Controls. 1	2	3
22	59	B. coli	Stool	20	17	25	10
22	60	Strep. non-hem.	Stool	15	5	15	0
22	61	Strep. non-hem.	Stool	20	0	0	5
22	62	Strep. non-hem.	Throat	15	5	0	0
22	63	Strep. hem.	Throat	16	6	8	5
22	64	Unidentified	Throat	10	0	5	0
23	65	M. catarrhalis	Throat	10	22	17	15
23	66	Strep. non-hem.	Throat	0	27	5	0
23	67	Strep. non-hem.	Tooth	0	0	0	6
24	68	Strep. non-hem.	Throat	0	3	8	5
24	69	B. coli	Stool	0	3	0	0
25	70	B. coli	Stool	27	0	7	6
25	71	Unidentified	Stool	15	10	6	5
25	72	Strep. non-hem.	Stool	0	0	6	0
25	73	Strep. non-hem.	Throat	0	0	7	4
26	74	Strep. non-hem.	Throat	0	3	4	0
27	75	Strep. non-hem.	Tooth	8	0	23	0
27	76	Strep. non-hem.	Tooth	10	0	15	0
27	77	B. coli	Stool	15	20	35	25
28	78	B. coli	Stool	27	27	17	0
28	79	M. catarrhalis	Throat	50	35	40	4
28	80	Strep. non-hem.	Throat	15	5	5	0
29	81	Staphylococcus	Throat	0	5	0	10
29	82	Strep. non-hem.	Throat	0	0	0	0
29	83	B. coli	Stool	0	4	8	10
30	84	B. coli	Stool	8	5	0	17
30	85	B. coli	Stool	15	17	8	22
30	86	Strep. non-hem.	Throat	5	6	0	0
31	87	Staphylococcus	Throat	25	5	27	10
31	88	Strep. non-hem.	Throat	22	0	2	0
32	89	Strep. non-hem.	Throat	7	13	3	6
32	90	Strep. non-hem.	Throat	5	5	2	3
32	91	Strep. non-hem.	Throat	14	6	2	3
32	92	Strep. non-hem.	Stool	5	0	0	4
32	93	B. coli	Stool	27	20	5	35
32	94	Strep. non-hem.	Tonsil	25	5	23	12
32	95	Strep. non-hem.	Tonsil	11	3	20	6
33	96	Strep. non-hem.	Throat	0	3	0	0
33	97	Strep. non-hem.	Throat	0	3	0	0
33	98	B. coli	Stool	0	5	0	27
33	99	Strep. non-hem.	Stool	0	0	0	9
33	100	Strep. non-hem.	Stool	0	0	0	0
34	101	Strep. non-hem.	Tooth	0	2	5	0
34	102	Strep. non-hem.	Tooth	5	2	4	0

Even in an acute disease like typhoid fever from the second week on, the blood usually possesses a strong bactericidal effect. In pneumococcic infections, to which Solis-Cohen refers repeatedly, the normal bactericidal effect of the blood usually persists for several days after the onset of the pneumonia.[15] Furthermore, in pneumonia patients with persistent foci of infection remaining after the healing of the pulmonary process, the development of the bactericidal property of the blood is not retarded.[16] We can see, therefore, that the examination of the bactericidal property of the blood may

be misleading, even in pneumococcic infections and that until direct evidence is brought forward showing that this method usually gives good results in diseases of known etiology, indirect evidence in obscure conditions is of little value.

We also regard with skepticism the results obtained by skin testing the patients with vaccines made from different bacterial strains cultivated from various sites. The specificity of a skin test can be established only by testing a strain on a large number of controls as well as on the patient. Reactions obtained with controls have usually not been examined in the skin tests thus far reported.

The interpretation of skin sensitiveness is simple in such diseases as tuberculosis, glanders, and certain fungus infections where a strong, specific sensitivity develops, but the interpretation of slight skin reactions is usually impossible. Such procedures as skin reactions with concentrated urines (Wildbolz[17] reaction) and with horse serum (Busacca[18] reaction) in tuberculosis were once believed to be specific enough to be used for diagnostic purposes. The effect of non-specific irritation, *e. g.*, the application of cantharides plaster, shows regular variations in the course of different infectious diseases.[19] Such observations must warn us not to accept without due criticism the specificity of a skin reaction. The determination of the etiologic relationship between a disease and a certain bacterium is usually a very difficult task and the history of bacteriology shows that assumptions made on an insufficient basis have usually proven false.

At this point, we would like to present our own experience with skin reactions, the study of which, beside their eventual application to vaccine therapy, appeared of interest because rheumatoid arthritis presents certain characteristics suggesting that allergy may play an etiologic rôle. Skin reactions usually have a wider zone of specificity than serologic reactions and so offer better chances for finding strains to which the patients are markedly sensitive. By controlling the skin reactions carefully by tests on several other subjects, we obtained essentially negative results. We shall give, therefore, a short description of them only in regard to the claims which have been offered that with the help of skin tests it is possible to obtain useful information in both the etiology and therapy of rheumatoid arthritis.

The technique used for preparation of the vaccines was as follows: Cultures were obtained on blood agar plates and in broth, and several strains of the different bacterial species were isolated on blood agar plates. The vaccines were made from cultures on plain or chocolate agar slants. The bacterial emulsion was standardized with the help of a barium sulphate suspension and, after heating for 1 hour between 58° and 60° C., 0.3 per cent tricresol was added. Skin tests were usually made with 0.05 cc. of the vaccine on the forearm of the patient and the three controls.

In all, 102 vaccines, obtained from bacteria isolated from 34 patients, were examined. Forty-seven vaccines were made from strains isolated from the throats of the patients. Of these, 36 were non-hemolytic streptococci (alpha and gamma types), the rest various throat organisms. Forty-one strains were isolated from stools, with 23 identified as B. coli and 14 as streptococci. Ten streptococcus strains were isolated from extracted teeth and 4 from excised tonsils. Four hundred and eight skin tests were made with these vaccines.

The results, as shown in Table 1, were essentially negative, as very few of the patients gave skin reactions which would indicate specific hypersensitiveness. A few strains (Nos. 61, 62, 64, 80, 88) gave definitely positive reactions (1 cm. or more), while all 3 controls gave insignificant tests. But a larger number (23) gave very slight reactions on the patients from whom they had been isolated, while at least 1 control gave a definitely positive reaction. We might expect this, according to the laws of chance, since the controls outnumbered the patients 3 to 1. One patient (Case 22) who reacted more strongly to 3 of the 5 above-mentioned "positive" strains, reacted to a whole series of streptococcus strains more strongly than most of the subjects tested, as well as to a colon bacillus strain. This patient was possibly hypersensitive to the Streptococcus viridans, although her stronger reactions may not have been specific at all. Another patient (Case 31) who reacted more strongly to his own streptococcus strain than the controls, reacted also to another streptococcus in the same way. A third patient (Case 2), who was tested with 5 autogenous and 21 heterologous vaccines, constantly gave negative (19 out of 26 (83 per cent)) or very slight reactions (average diameter 0.2 cm.). A non-specific fluctuation of the irritability of the skin and possibly a sensitization to certain bacterial groups would seem to account for the variation in the strength of the skin reactions.

Another interesting finding was that certain bacterial species, regardless from whom isolated, tended to give large reactions. This is illustrated by the table below, where the results obtained with B. coli and M. catarrhalis are compared with the strains of non-hemolytic streptococci from throats and stools.

TABLE 2.—SKIN REACTIONS WITH DIFFERENT ORGANISMS.

Strain.	Source.	Number of tests.	Per cent 1 cm. or more.	Average diameter in millimeters.
B. coli	Stools	92	52	13.0
M. catarrhalis	Throat	12	92	23.0
Streptococcus non-hem.	Throat	144	16	4.5
Streptococcus non-hem.	Stools	56	27	5.0

This striking difference was most likely due to what may be called the natural toxicity of the bacterial species concerned.

As half of our controls were patients with arthritis, our observations allow no conclusion as to the presence of hypersensitiveness to Streptococcus viridans in arthritic patients. The majority of patients gave slight or no reaction to the relatively large doses of vaccine which we used. However, if we take the group of arthritics as a whole, whether controls or not, 24 per cent showed reactions greater than 1 cm. in diameter and 10 per cent 2 cm. or greater. In comparison, 17 per cent of the non-arthritic gave reactions 1 cm. or more and only 3 per cent 2 cm. or greater. Myers *et al.*[20] concluded that patients with rheumatoid arthritis gave stronger reactions to nucleoproteins of Streptococcus scarlatinæ, whereas Derick and Fulton[21] discovered only slight differences with nucleoproteins from hemolytic and green streptococci in comparing normals with an arthritic group of unspecified type. MacKenzie and Hanger,[22] using derivatives of hemolytic and green streptococci, found no relationship between positive skin reactions and any one disease or group of diseases.

From our results and those cited above, we feel that there is certainly no allergy to streptococci as shown by skin reactions present in the arthritic patient comparable in strength to the allergy developing in tuberculosis and certain other chronic infectious diseases. One of the authors (C. L. S.) after repeated skin tests on himself, developed a marked skin reaction to Streptococcus viridans, giving stronger reactions than any of the patients. In those diseases where allergy plays an important rôle, the allergy developing in the disease is usually much stronger than the allergy developing after vaccination.

Summary and Conclusions. 1. Skin tests made with bacterial strains isolated from arthritic patients do not allow us to select specific strains for vaccine therapy.

2. Skin tests without using several subjects as controls are without any significance.

3. Variations in the skin reactions may be explained by differing irritability of the patient's skins, natural toxicity of the bacterial species, or possibly by a sensitization to certain bacterial groups.

4. The different methods which have been recommended for the selection of specific vaccine strains are without a solid theoretical or experimental foundation.

5. The above conclusions suggest that the therapeutic effect, if any, gained from autogenous vaccines is non-specific.

6. The hypothesis that rheumatoid arthritis is a disease of allergic origin is not supported by conclusions drawn from the interpretation of uncontrolled skin reactions with autogenous vaccines.

REFERENCES.

1. Freiberg, J. A.: Arch. Surg., **18**, 645, 1929.
2. Klinge, F.: Klin. Wchnschr., **6**, 2265, 1927.
3. Klinge, F.: Beitr. path. Anat., **83**, 185, 1929.

4. Vaubel, E.: Beitr. z. path. Anat. u. z. allg. Path., **89**, 374, 1932.
5. Gudzent, F.: Personal communication.
6. Freiberg, J. A., and Dorst, S. E.: J. Lab. and Clin. Med., **15**, 1109, 1930.
7. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J.: Arch. Int. Med., **43**, 571, 1929.
8. Gray, J. W., and Gowen, C. H.: Am. J. Med. Sci., **182**, 682, 1931.
9. Nye, R. N., and Waxelbaum, E. A.: J. Exp. Med., **52**, 885, 1930.
10. Dawson, M. H., Olmstead, M., and Boots, R. H.: Arch. Int. Med., **49**, 173, 1932.
11. Schottmüller, H.: München. med. Wchnschr., **76**, 445, 1929.
12. Burbank, R., and Hadjopoulos, L. G.: J. Am. Med. Assn., **84**, 637, 1925.
13. Shuster, M.: Med. J. and Rec., **134**, 347, 399, 1931.
14. Solis-Cohen, M., and Rubenstone, A. I.: J. Lab. and Clin. Med., **11**, 881, 1926.
15. Robertson, O. H., Terrell, E. E., Graeser, J. B., and Cornwell, M. A.: J. Exp. Med., **52**, 421, 1930.
16. Finland, M., and Sutliff, W. D.: Ibid., **54**, 637, 1931.
17. Wildbolz, H.: Cor.-Bl. f. schweiz. Aerzte, **49**, 793, 1919.
18. Busacca, A.: Wien. klin. Wchnschr., **34**, 570, 1921.
19. Kauffmann, F.: Krankheitsforschung, **2**, 372, 1926.
20. Myers, W. K., Keefer, C. S., and Oppel, T. W.: J. Clin. Invest., **12**, 279, 1933.
21. Derick, C. L., and Fulton, M. N.: Ibid., **10**, 121, 1931.
22. MacKenzie, G. M., and Hanger, F. M., Jr.: J. Immunol., **13**, 41, 1927.

SPECIFIC TREATMENT OF SEPTIC INFECTIONS, PARTICULARLY WITH AID OF BACTERIOPHAGES.*†

By Ward J. MacNeal, M.D.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL, COLUMBIA UNIVERSITY, NEW YORK CITY.

The temporary invasion of the blood stream by infectious microorganisms is doubtless of frequent occurrence and in malaria, relapsing fever, typhoid fever or lobar pneumonia it may present no particular reason for alarm. However, when a positive blood culture shows Staphylococcus aureus, Escherichia coli, Streptococcus hemolyticus or Streptococcus viridans, the vision of a fatal septicemia comes even to the optimistic physician. Many of these patients might have escaped such a grave complication if their infection had received adequate attention while still a localized disorder before invasion of the blood stream. A considerable part of regional surgery is directed to forestall just this catastrophe by providing external drainage or local antiseptic treatment of the infected region.

Unfortunately, it seems to me, there has been a relative neglect of specific bacteriologic diagnosis in some of these local surgical conditions. American surgeons are, in general, aware of the need for a gross and microscopic pathologic study of tissues which they remove from the patient, but as yet seem not to sense fully the

* These studies have been supported in part by a grant from the Josiah Macy, Jr. Foundation.

† Read before the Section on Pharmacology and Therapeutics, American Medical Association, Milwaukee, June 16, 1933.

importance of a bacteriologic study of inflammatory lesions and exudates. The therapeutic measures of drainage and chemical disinfection are not uncommonly assumed to apply with equal efficiency to all such lesions, so that specific recognition of the microbic parasite is considered to be a superfluous refinement. All will grant the value of knowing when an abscess contains bacilli of anthrax or of bubonic plague or of gas gangrene, but these infections are so unusual with us that we take the chance. I wish to plead the importance of specific diagnosis in the more common inflammatory exudates and wound infections, the importance of recognizing such common microbic parasites as the staphylococci, the streptococci, the various types of pneumococci, the hemoglobinophilic bacilli of Pfeiffer and of Ducrey and the Klebs-Loeffler bacillus. Efficiency in treatment of the patient can hardly suffer because of accurate knowledge of this kind and not infrequently it may be helpful to know the specific nature of the infectious agent.

This is emphatically true when one wishes to employ a specific antiserum as against the diphtheria bacillus or against a particular type of pneumococcus or against a streptococcus. It is also emphatically true when one attempts to employ such specific lytic agents as the bacteriophages. These peculiar bacteriolytic agents[1] act efficiently against only particular bacterial species and sometimes only against particular varieties within the species. The early specific bacteriologic diagnosis and the early application of the therapeutic measures effective against that specific type of infection either alone or in conjunction with proper local incision, excision and chemical disinfection may often suffice to ward off the danger of septicemia. On the other hand not inconsiderable numbers of septicemias are recognized subsequent to local surgical incision or excision undertaken without due regard to and often without previous recognition of the nature of the infecting microbe.

When the local inflammatory lesion is associated with a temperature reaching 103° F. or higher on 2 or 3 days or presenting marked sudden temperature elevations associated with rigors and rapid depressions associated with diaphoresis, one should not hesitate too long before subjecting the blood to a microscopic and a cultural examination. The blood count and malaria search are commonly asked for, but it is really astounding to observe the period of septic fever which may sometimes be recorded on the bedside chart, even in some of our large hospitals, before a blood culture is made. Perhaps the physician may excuse his inaction here by a desire to avoid frightening the patient or perhaps because he himself does not wish to know the truth on account of his generally hopeless outlook in septicemia. For this latter attitude I see no defense. As for frightening the patient, the taking of blood for culture may be readily camouflaged and even a physician patient may be mislead to think that the specimen is being taken for chemical analysis, sero-

logic test or for careful and elaborate matching of blood for transfusion. In general, however, there is no real need for deception and the patient himself will often manifest a keen interest in his blood culture without fully sensing its grave significance.

During the last few years my associates and myself have been particularly interested in a study of the possible value of bacteriophages in the treatment of septic infections and in an attempt to learn how to use these agents so that they may be helpful. Given a bacteriophage which will completely destroy the bacterial culture in the test tube, it is easy to hope that it may be equally effective in eradicating the same bacteria from the body of the infected patient. In this we have been doomed to disappointment. The interaction between bacterial growth and specific bacteriophage is evidently subject to wide variations and influenced by many environmental factors. Temperature, acidity[2] or alkalinity of the medium, presence of blood, blood serum[3] or inflammatory exudate and the presence of an antiseptic chemical may be sufficient to impede the lytic action of the bacteriophage and permit the overgrowth of the bacteria even in the test tube. In the body of the patient some of these agents, as well as others still unrecognized, may be expected to interfere. In fact by a logical consideration of the results of experiments in the test tube one may quite reasonably arrive at the conclusion that no bacteriophage effect can be expected to occur in the living body.[4] This conclusion has its supporters just as there are enthusiasts of the opposite extreme opinion.[5] Actually, however, the matter cannot be settled by argument and discussion. Clinical trial, subject to many inaccuracies, must nevertheless furnish the final answer as to the value of bacteriophage therapy.

My colleagues and I have had the opportunity to observe the clinical application of bacteriophages in a considerable number of patients and have been privileged to prepare the bacteriophages and carry out the laboratory procedures for a great many more. We have come to feel that the antistaphylococcus bacteriophage, made in a broth medium for local application and in an asparagin medium for injection into the tissues or into the circulating blood, has already been established as a valuable therapeutic agent, not only in local staphylococcus infections, as in wounds, boils,[6] carbuncles and osteomyelitis, but also in staphylococcus bacteremia.[7] Our enthusiasm for this agent has not diminished at all with continued experience in its use. When the local lesion is easily accessible it is well to irrigate it with the bacteriophage and to apply the latter as a wet dressing. Injections are also made into the tissues about the margin of the lesion and, in case of a boil, injection through a very fine needle into the base of the lesion may be employed to wash out the pus through a small opening at the center. At the same time subcutaneous injections should be given at a distant site, about twice

a week, as a vaccine. When the lesion is deeply situated, as in actively progressive osteomyelitis, abscess of kidney or multiple early abscesses of the lungs, the intravenous injection is the method of choice. In staphylococcus bacteremia, the intravenous treatment is now invariably recommended and employed by us, together with application of bacteriophage locally if the primary lesion is superficial or easily reached. In these patients after a preliminary blood culture, we begin with a small dose, as a rule, 0.5 cc. of undiluted asparagin bacteriophage, or preferably 5 cc. of a 1 to 10 dilution of this, intravenously. After 40 min. 1 cc. of the undiluted preparation is given and after another 40 min. 2 cc. This procedure is continued, doubling the dose each time until one reaches the dose of 8 or 16 cc. or until the patient presents the signs of a shock reaction. We have given in this way as much as 70 cc. intravenously within 24 hr. and we have record of 1 patient, a child, who received 140 cc. within 24 hr. without serious effect. In most patients, however, a definite reaction will appear fairly early, often after a total amount of 3.5, 7.5 or 15.5 cc. has been given. Approximately 25 to 35 min. after an injection the patient goes into a chill which may be severe. It is well to be ready with warm external applications and with oxygen for the relief of dyspnea and cyanosis. The internal temperature rises rapidly and at the end of a chill of 20 to 30 min. it is usually between 104° and 106°. Sweating and rapid fall in temperature to 99° or below follow in an hour or so and the temperature begins to rise again after about 12 to 20 hr. We regard this reaction as favorable. The patient who fails to react will sometimes have yielded a sterile blood culture immediately before the injections were started. On the other hand the patient in whom the blood culture is positive tends to develop this shock reaction. If he does not, the outlook is in our experience unfavorable.

After the reaction, small intravenous injections of bacteriophage, 1 to 4 cc., should be continued daily for several weeks, even though the blood culture has become negative. Neglect of this has, in some instances, been followed by undesirable metastatic abscess. However, there is a possibility that too prolonged bacteriophage therapy may be associated with progressive emaciation.

Localized purulent lesions should receive appropriate surgical attention, but one can afford to be far more conservative in the use of excision and incision than he would be in a staphylococcus infection not receiving bacteriophage. The experienced surgeon who deals with a few of these patients quickly recognizes the difference in behavior and modifies his surgical technique to meet the new situation.

In one instance we have treated a purulent collection, situated in a bursa on the back of the left hand over the fourth and fifth metacarpals, by immobilization and aspiration and irrigation with bacteriophage through the needle and later by irrigation through one

A

B

FIG. 1.—Hands of L. S., photographed March 29, 1933. The site of most severe earlier inflammation is indicated by the thickened skin. On March 6, 1933, the patient presented himself with a fluctuating prominence surrounded by swollen red area covering the dorsum of the left hand. Aspiration obtained thick hemorrhagic pus which, on culture, yielded Staphylococcus aureus. On March 8 the cavity was again aspirated and irrigated 6 times with bacteriophage, being left in the collapsed state. This treatment was repeated on March 10 and 13. On March 15 the cavity was punctured with two needles and washed through with 6 cc. of asparagin bacteriophage. This treatment was repeated on March 16, 17, 18 and 20. The fingers were fixed by wooden splint until March 18, but after that time free movement was permitted. Cultures of the thin exudate obtained on March 20 remained sterile. The patient also received immunizing dose of 1 cc. bacteriophage into the deltoid region on March 6, 10, 15, 22 and 25. He remained at work all the time and the functional result has remained perfect.

needle with outlet through a second larger needle. At first the cavity yielded thick blood-tinged pus showing Staphylococcus aureus on culture. The last aspiration yielded a minute drop of pink fluid, cultures of which remained sterile. The hand has healed without incision, scar, disability or deformity (Fig. 1).

Osteomyelitis is a frequent sequel of staphylococcus bacteremia, particularly in young persons. Intravenous bacteriophage therapy is useful in limiting the extension of the process during the earlier stages and local applications of bacteriophage after surgical drainage are helpful in promoting favorable progress. In collaboration with orthopedic surgeons, particularly Albee,[8] Carter and Gratz, we have had opportunity to become wholly convinced of the value of bacteriophage in staphylococcus infections of bone. As an example of this type of infection a brief summary of a case which terminated in death after a period of 4 months is presented. The clinical chart for this period is so extensive that its reproduction has been deemed inadvisable.

Case Report.—M. H., schoolgirl, aged 17, developed osteomyelitis of the right innominate bone, beginning on December 16, 1932. This extended to involve the entire ilium, part of the ischium and the hip joint. There was also serous arthritis of the right knee and a rounded spot of rarefaction in the upper right tibia. Her first operation was performed on December 28 at another hospital. Upon admission to this hospital on January 19, she was desperately ill. Blood culture taken soon after admission yielded four colonies of Staphylococcus aureus per cc. of blood. That evening the soft parts over the hip were incised and a small amount of the diseased bone removed. Cultures were inoculated from the exudate. At the same time a transfusion of 200 cc. was given. The next morning it was possible to recognize colonies of staphylococcus in the cultures from the diseased tissue. At the request of the surgeon, Dr. C. M. Gratz, bacteriophage treatment was begun. A dose of 1 cc. antistaphylococcus asparagin bacteriophage was given intravenously and 12 cc. of the broth preparation of the same was injected into the single rubber drain. On January 21, the growth in the blood culture of January 19 was first recognized and it was decided to push the intravenous treatment to a shock reaction. A blood culture was taken, which remained sterile, and then at 11 A.M. the series of intravenous bacteriophage injections was begun, 2, 4, 8 and 10 cc. being given at 11 A.M. 12 NOON, 1.22 and 2.45 P.M. respectively, the total amount being 24 cc. The chill began at 3.52 P.M. and lasted 22 min. and the temperature rose to 106 at 4.15 P.M., quickly falling to 99 at 8 P.M. On January 22 and 23 the dose of intravenous phage was 4 cc. on each day and after that 2 cc. daily to January 28. The broth preparation was injected into the drain daily. The patient did well. Her temperature remained below 102° except on January 25 and 26, following a transfusion on January 25.

On February 20, under ether anesthesia, the plaster dressing was completely removed, the wound was revised, position of the right lower extremity changed, the right knee joint aspirated and a new extensive plaster dressing applied over vaseline pack, with two rubber catheters left in the wound, one with its opening within the capsule of the hip joint and the other in contact with the ilium. These catheters were brought out through the anterior part of the plaster. Dependent counter drains were left extending posteriorly through the buttock. The knee joint was left closed and the aspirated fluid gave negative cultures. The tibia was not incised. The

plaster dressing, however, was carried all the way down to include the toes of the right foot and the ankle of the left foot.

The patient did not do so well after this operation. Blood culture taken the next day gave delayed positive growth of staphylococcus in one broth flask while a second flask and three plates remained sterile. On February 24 the drainage from the wound yielded abundant colonies of colon bacilli and some hemolytic streptococci. Anticolon bacillus bacteriophage was therefore added to the staphylococcus phage put into the two drains on February 27. Now hemolytic streptococci and the bacillus of green pus appeared in abundance on the cultures from the exudate and on March 2 the antipyocyaneus bacteriophage and our feeble antistreptococcus phage were called into play. However, there appeared a marked dermatitis, suggesting erysipelas, on the skin visible beneath the upper margin of the plaster dressing and it was considered unwise to withhold the streptococcus serum. The concentrated streptococcus serum of the New York State Department of Health was injected, at first in small intracutaneous and subcutaneous doses and then in larger intramuscular doses, 20,000 units on each of 4 days, March 4, 5, 6, and 7. Subsequently, urticaria and vomiting complicated the clinical picture. The intravenous staphylococcus phage was continued, as also the mixture of 3 or 4 broth phages into the drains. Nutrition became a problem and emaciation progressed. Hormone injections, eschatin and insulin, were used in the hope of a favorable influence. Blood cultures on February 28, March 23, April 6 and 15 remained negative. Eventually on April 14 the vomiting became so persistent that the patient was becoming dehydrated, with acetone breath and acetone in the urine and pitiable emaciation. The intravenous bacteriophage dosage was now reduced and after April 16 it was discontinued. Glucose salt solution was given intravenously on April 15 and 18, and on April 18 a duodenal tube was passed through the nose for forced feeding. This tube remained in place until the morning of April 22, by which time the patient had visibly gained flesh and strength and was again able to take food in the natural way and to retain it.

Meanwhile the hip had become fixed and much of the plaster dressing had been cut away. The patient could be turned onto her side and onto her face without pain and it was possible to remove and renew the padding under the plaster.

On April 24, under avertin and nitrous oxid, the dressings and drains were removed, roentgenograms were made which showed favorable progress of the bone lesions, and the wounds were distended and dressed and a new plaster dressing applied. Following this there was again persistent vomiting and the duodenal tube was again introduced on April 27. The posterior drainage opening were revised and enlarged on May 2 and 3 and the exudate revealed predominant hemolytic streptococci. Streptococcus serum was given, 60,000 units from May 4 to May 6 and saline irrigation to the drains was substituted for bacteriophage mixture, as the latter was not effective against streptococcus. Progressive emaciation, intractable diarrhea and a terminal aspiration pneumonia continued to death at 1.40 A.M., May 17. Necropsy was not permitted.

This case illustrates the influence of the staphylococcus bacteriophage, even though the patient did not survive. The infection of the blood stream was overcome and the lesions in right tibia and right knee joint receded without surgical drainage. In the ilium and the hip joint, secondary infection with other bacteria, particularly streptococci, appeared to be responsible for the ultimate failure.

Blood stream infection with the streptococci is one of the common types of septic infection. The hemolytic streptococcus extends from primary lesions in nose, throat, ear or uterus into the walls and lumina of altered veins and eventually into the circulating blood. Up to the present time we have had no success in our attempts to apply the bacteriophage phenomenon to the treatment of such conditions. On the other hand we are convinced that the vigorous efforts to improve the quality of antistreptococcus serum obtained

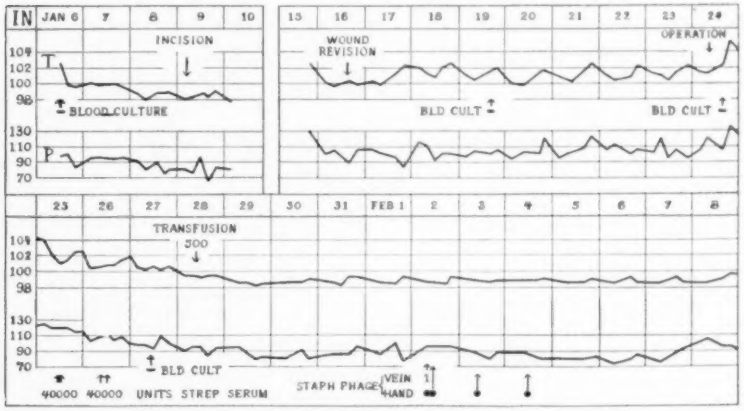

CHART I.—Abridged record of I. N., a student nurse aged 20, who had chapped hands on January 1, 1933, and on January 5 a severe throbbing pain in the left hand extending up above the left elbow. On the morning of January 6 the hand was dressed by a surgeon and subsequently the patient vomited and became unable to remain on duty. She was admitted to the hospital at noon with diagnosis of furuncle and complicating cellulitis. Blood culture taken on admission remained negative. She was discharged on January 10 and again admitted as patient on January 15. On January 24 the left axilla was incised by Dr. John F. Erdmann and a second large purulent collection on the right side of the neck was opened. In both these regions there was abundant hemorrhagic pus. The aid of specific treatment was at once requested by Dr. Erdmann. The axillary and cervical pus contained abundant streptococci, but no staphylococci. Concentrated streptococcus serum of the New York State Department of Health was given on January 25 and 26, a total of 80,000 units, and a transfusion on January 28. Improvement was prompt. The hand, however, was not doing so well and here the exudate contained staphylococci. A single intravenous dose of asparagin staphylococcus bacteriophage was given on February 2 and wet dressing of the broth phage was applied on February 2, 3 and 4, with prompt healing.

from immunized horses have, in recent years, succeeded in the production of serum really potent against these streptococci. So far we have had a few successes in frank septicemias treated with such serum and we have observed some remarkably quick recoveries, after use of the concentrated experimental antistreptococcus serum of the New York State Laboratory, in streptococcus infections of the hands with lymphatic extension to form axillary abscesses, particularly in physicians, nurses and in laboratory personnel (Chart I).

Endocarditis lenta, with vegetative lesions on the valves of the

heart and persistent Streptococcus viridans in blood culture, is a chronic septicemia, which has engaged our attention for some years. Our attempts to apply the bacteriophage phenomenon[9] in treating this disease have been followed by some diminution of our self assurance as well as death of our patients. However, the field has not been abandoned.

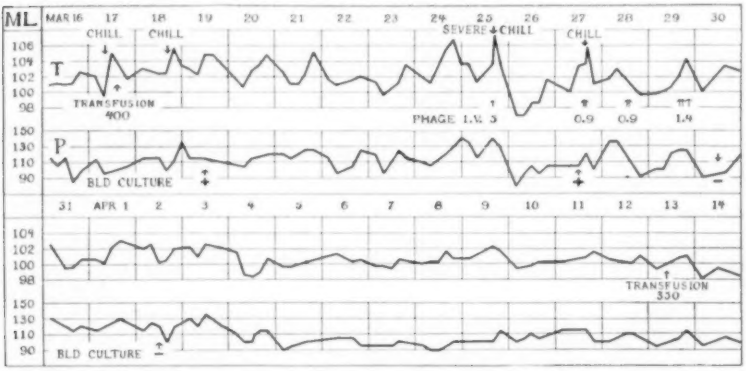

CHART II.—Abridged record of M. L., white female aged 21, admitted March 15, 1931, suffering from pelvic thrombophlebitis and colon bacillus septicemia following abortion about March 1 and curettage about March 3. This patient has been mentioned in some of our previous papers but the clinical record has not been previously presented. Blood culture on March 19 yielded colon bacilli and this organism was found susceptible to lysis by bacteriophage available in the laboratory. However, its use was not invited until the temperature had reached 106.8° on March 24 and the condition was considered hopeless. It was decided to begin with a series of intravenous injections of the asparagin preparation spaced at 40 min. and the initial dose of 5 cc. was given about 4.30 P.M. on March 25. The shocking reaction which followed within ½ hr. prevented further injections. After a chill lasting from 4.50 P.M. to 5.20 P.M., the temperature reached 107.2° at 5.20 P.M. This was followed by profuse diaphoresis and apparent collapse which continued until noon of the next day. The expected exitus failed to take place and on March 27 after taking a blood culture we were bold enough to start again with an intravenous dose of 0.5 cc. at 3.05 P.M. followed by a second dose of 0.4 cc. at 3.42 P. M. Just as the arm was being prepared for the third dose at 4.15 P.M. the patient went into a rigor which lasted until 4.26 P.M. when her temperature was 105.8°. On March 28 two more intravenous injections were given, 0.5 cc. at 1.35 P.M. and 0.4 cc. at 2.10 P.M., without evident reaction, and on March 29, 3 intravenous injections, 0.5 cc. at 4 P.M., 0.4 cc. at 5.40 P.M. and 0.5 cc. at 8.15 P.M. No further bacteriophage was administered. Blood cultures, taken on March 30 and on April 2, remained negative.

On April 3, after a fit of coughing the patient complained of pain in the chest and upon physical examination and roentgenologic study a right spontaneous pneumothorax was discovered. The lung was compressed except near the diaphragm where it was held by a thick adhesion. Apparently there was an old tuberculous process here. With rest in bed the lung expanded again and the pneumothorax disappeared. On April 13 she was transfused with 350 cc. of blood at 9.30 A.M. On April 22 the patient was allowed out of bed and on April 28 she was discharged from the hospital. Her right leg remained slightly larger than the left as a sequel to the edema which had otherwise subsided. There was no other recognizable evidence of her illness.

Blood stream infection with paratyphoid and paracolon bacilli occurs in food poisonings and in the paratyphoid fevers without necessarily grave significance. Septicemia due to the colon bacillus,

however, seems to be more serious. It appears to come from ascending pyelonephritis and from septic wound infections and is frequently a terminal phenomenon, if one may judge by bacteriologic findings at early necropsy. We have employed bacteriophage in the treatment of 3 septicemias due to colon bacilli and have supplied the bacteriophage for treatment of a fourth patient in this category in another hospital. The anticolon bacillus bacteriophage prepared in the asparagin medium was injected intravenously in all four. One died after repeated large doses without a very definite reaction and with persistent positive blood culture. Another patient with a septic thrombosis of the pelvic veins following abortion suffered a frightful shock from the first intravenous dose of bacteriophage, reacting with a chill and temperature rise to 107.2°. She made a complete recovery (Chart II). In the other 2 patients the reactions were mild, the septicemia disappeared but the infection of the urinary tract remained. One of these patients refused to bother with further treatment after her serious symptoms were relieved. In the other, the persisting infection of the urinary tract was complicated by pregnancy which had not been interrupted by the septicemia. However, 10 days after bacteriophage treatment had been discontinued the fever returned, followed, after 72 hr., by premature labor and the birth of a 6-months fetus which survived for an hour. Since then the patient has become clinically well but the urine still contains pus cells and numerous colon bacilli.

The use of bacteriophages in the treatment of localized colon-bacillus infections, such as those of the urinary tract, external wounds and intestinal lesions has been found distinctly helpful in a large proportion but not by any means in all the cases. Rather elaborate laboratory studies are required in order to select the most promising among the bacteriophages for each particular infection and to get ready the most effective preparation of the bacteriophage selected. Unfortunately the colon bacilli are not always found susceptible to lysis by the races of bacteriophages in our possession. However, when it is possible to get a bacteriophage fully potent against the particular colon bacillus and to employ it with intelligence and skill, its therapeutic value compares well with that of the staphylococcus bacteriophages in their therapeutic field.

Comment. The summarized records of 4 patients here presented have been selected to illustrate some of the ways in which we have attempted the specific treatment of infection. The cellulitis and bursitis of the hand illustrated in Fig. 1 was not a desperate condition. The technical procedure of irrigation was tried on this patient with the idea that we might later use a similar principle in treating a purulent pericarditis or a purulent arthritis. The other 3 patients have been selected because they appear to illustrate a favorable influence of specific treatment by bacteriophages or by serum in

patients very seriously ill. Unfortunate cases with early fatal termination have not been included in the brief series here discussed and it is hoped that no one will be deceived by this omission. Such fatalities will be found recorded in the more detailed publications from our laboratory.

It will be observed that we have not relied exclusively upon serum or upon bacteriophage but have employed these agents in conjunction with, and as aids to, other therapeutic measures. Furthermore the nature, variety and quantity of clinical material which has become available for our experimental therapy has not permitted setting aside untreated controls. Many of the moribund patients might be left to make such a control group but this would not be fair nor justified either as scientific or humanitarian. The present purpose is not, therefore, to present proof that the use of specific serum or of specific bacteriophage decides the issue between life and death in human beings. In fact we assume that such proof will not be required by the sympathetic observer and cannot at present be furnished in sufficient strength to convince the unsympathetic skeptic. There can be no doubt, however, that these agents are capable of causing changes in the condition of the patient and in the course of his disease. Knowledge of their action, care and skill in their use, coupled perhaps with good luck, may sometimes contribute to the fortunate outcome of an illness otherwise without good prognosis.

In conclusion, I would say that effective therapeutic application of bacteriophages, as well as effective use of therapeutic serums, requires an intimate and sympathetic coöperation between the workers at the bedside and the workers in the laboratory, most perfectly realized when the same persons consult together in both places, studying together the behavior of the patient and the behavior of the cultures. The use of commercial preparations of bacteriophages leaves much to be desired in this particular respect and is not free from other important objections.[10] In general the attempts at wholesale commerical exploitation of these agents is, in our opinion, to be deprecated at the present time.

Summary. 1. The early specific diagnosis of infectious disease by immediate application of the appropriate bacteriologic technique is strongly urged.

2. Specific diagnosis facilitates proper care of the patient and isolation of the specific microbe makes possible the intelligent selection of specific serum or specific bacteriophage.

3. The appropriate application of antistreptococcus serum or of bacteriophages against the staphylococcus or the colon bacillus requires intimate collaboration of clinician and laboratory worker. The use of these agents is recommended as beneficial to some patients suffering from infection with the respective microbes.

REFERENCES.

1. Twort, F. W.: Lancet, **2**, 1241, 1915.
2. Frisbee, F. C., and MacNeal, W. J.: Proc. N. Y. Path. Soc., Arch. Path., **9**, 1116, 1930; J. Inf. Dis., **46**, 405, 1930.
3. Applebaum, M., and MacNeal, W. J.: Proc. N. Y. Path. Soc., Arch. Path., **11**, 680, 1931; J. Inf. Dis., **49**, 225, 1931.
4. Krueger, A. P., Lich, R., Jr., and Schulze, K. R.: Proc. Soc. Exp. Biol. and Med., 1932, **30**, 73; Northrup, J. H., and Krueger, A. P.: J. Gen. Physiol., **15**, 329, 1932.
5. D'Herelle, F.: The Bacteriophage and Its Behavior, Williams and Wilkins, Baltimore, pp. xiv + 629, 1926; Bull. New York Acad. Med., **7**, 329, 1931; The Bacteriophage and Its Clinical Application, Baillière, Tindall & Cox, London, and Charles C Thomas, Springfield, Ill., pp. vii + 254, 1930.
6. Cipollaro, A. C., and Sheplar, A. E.: Arch. Dermat. and Syph., **25**, 280, 1932.
7. MacNeal, W. J., and Frisbee, F. C.: J. Am. Med. Assn., **99**, 1150, 1932.
8. Patterson, M. B., and Albee, F. H.: Proc. Soc. Exp. Biol. and Med., **27**, 376, 1930; Albee, F. H.: Am. J. Surg., **15**, 228, 1932.
9. MacNeal, W. J., Straub, M. E., and Spence, M. J.: Proc. New York Path. Soc., Arch. Path., **16**, 163, 1933.
10. Applebaum, M., and Straub, M. E.: Proc. New York Path. Soc., p. 28, 1932; Arch. Path., **13**, 685, 1932; Straub, M. E., and Applebaum, M.: J. Am. Med. Assn., **100**, 110, 1933.

THE RACIAL FACTOR IN PERNICIOUS ANEMIA: A STUDY OF FIVE HUNDRED CASES.

By Richard D. Friedlander,

ASSISTANT RESIDENT PHYSICIAN, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASSACHUSETTS.

(From the Medical Clinic of the Peter Bent Brigham Hospital.)

Although it has been the impression of clinicians for some years that pernicious anemia is a disease for the most part confined to the temperate zones and more particularly North America, the British Isles and Northern Europe, there has been doubt in the minds of some that race plays a definite rôle in the distribution of the disease. It has been suggested that patients from various parts of the different continents are attracted to centers where they are more likely to receive the best treatment in the hands of certain highly trained clinicians and, for this reason, the incidence of many other diseases as well as pernicious anemia is relatively higher in regions around these particular centers.

The first satisfactory statistical evidence in favor of definite racial discrepancies in the incidence of this disease appeared in 1921 as a result of a clinical study of 150 cases of pernicious anemia by Levine and Ladd.[1] An analysis of their group study indicated a lower frequency among Italians, Russians, Jews and immigrants from Eastern Europe as compared with a definitely higher percentage of cases among North Americans, Canadians and immigrants from Ireland, England, Sweden and Denmark.

The purpose of this survey is to confirm as far as possible the sug-

gestive findings of the above mentioned authors with a larger group of cases, employing the statistical data obtained from a study of 500 case histories of patients with typical pernicious anemia.

Information concerning this subject in the better known textbooks and systems of medicine is meager. French,[2] Bunting[3] and Cabot[4] found no restriction of the disease to any particular nationality. McCann and Maitland-Jones[5] remark the high incidence among the white race, particularly those of Nordic origin. Panton, Maitland-Jones and Riddock[6] in a clinical analysis of 117 cases of pernicious anemia noted that all were of English descent with the exception of 1 German and 6 Hebrews. Montgomery[7] studied a group of 320 cases occurring in patients from the Canadian provinces of Alberta, Saskatchewan and Manitoba and found, despite the inhabitation of these areas by a large French, Belgian and German population, practically all of his patients were blonds of Anglo-Saxon and Scandinavian heritage except for 2 Germans and 1 Pole. Cornell[8] states that it has been recognized for some time that Michigan, Ontario, New Brunswick and the eastern township of Quebec show high rates of incidence. This author quotes figures showing the high mortality rates for this disease in the United States, Denmark, Sweden and the Canadian provinces of British Columbia, Nova Scotia, Quebec and Ontario up to 1924. Binswanger[9] reviewed 230 cases occurring between the years 1900 and 1926 finding no difference in the morbidity in Germany, Austria and Switzerland. No outstanding racial tendency was observed other than that Hebrews comprised a very small number of the group and that the disease incidence was greater in Sweden and Finland than in Germany.

The rarity of pernicious anemia in North American negroes has long been recognized. Cornell[8] quotes Longcope that the disease seldom, if ever, affects full-blooded negroes. Carr[10] reported an incidence of about 5% in a group of 134 cases. Willson and Evans[11] reported 8 mulattoes in a clinical study of 111 cases. Jamison[12] found 54 cases of pernicious anemia among 122,524 admissions for all causes to the Charity Hospital in New Orleans during the period 1920 to 1926; of these 12 (29%) were negroes, a rather high figure considering the low incidence of the disease among the white race in the South.

Of 256 patients with the disease in the Cook County Hospital from 1921 to 1926 Traut[13] found an unusually large number of Scandinavians and Poles. During the period of this study about 33% of the total admissions were colored, but only 8 of these had the disease. Matthews[14] emphasizes the low incidence among negroes with the statement that only 28 cases are to be found reported in the literature up to 1929. Of 4940 total admissions to the United States Veterans' Hospital in Tuskegee, Alabama, during a 5-year period ending in 1928, only 2 negroes were diagnosed as

having the disease. Pernicious anemia in natives of tropical and oriental countries is extremely uncommon according to Morris,[15] Mills,[16] Yang and Keefer[17] and Williams.[18]

Mortality statistics, reported by Mills,[19] show the death rate from this disease to be definitely higher in Ireland, Scotland, Canada, England, Wales, United States, Norway, Netherlands, New Zealand and South Africa as compared with Italy, Uruguay, Barbados, Nigeria, the Philippines, Hawaii, Straits Settlements, Iceland, Haiti, and Ceylon. In the United States this author finds the mortality high in the areas centering around the Great Lakes Region and Northern California and a comparable area in Europe embracing the British Isles, Netherlands, Denmark and Northern Germany. Recently, Sturgis and Isaacs,[20] in a group of 580 patients, noted the incidence to be significantly greater in English-speaking people and Scandinavians than in immigrants from Russia, Italy and Eastern Europe.

Analysis of Peter Bent Brigham Hospital Data. From April, 1913, to November, 1932, 80,415 patients were admitted to this hospital for all causes, among which over 500 cases were diagnosed as pernicious anemia. For the purposes of this study 500 cases exhibiting only the typical manifestations of the disease were chosen.

FIG. 1.—TABULATION OF DATA.*

	All countries.	United States.	Total foreigners.	Russia.	Canada.	Ireland.	England.	Italy.	Scotland.	Germany.	Greece.	Sweden.	Denmark	Miscellaneous.	Negro.	All foreign countries except Canada, Ireland, England, Sweden, Denmark and Scotland.
Total admissions .	80,415	47,203	33,212	7559	7157	6272	2814	2332	1593	1206	1126	965	160	2928	4503	14,251
Per cent of total admissions . . .	100	58.7	41.3	9.4	8.9	7.8	3.4	2.9	1.9	1.5	1.4	1.2	0.2	2.7	5.6	17.9
Total number of P. A. cases . .	500	291	209	14	81	47	25	4	7	5	0	12	2	9	3	32
Per cent of P. A. cases	100	58.2	41.8	2.8	16.2	9.4	5.0	0.8	1.4	1.0	0	2.4	0.4	1.8	0.6	6.4
Per cent of P. A. cases among total admissions from various countries	0.62	0.61	0.62	0.18	1.1	0.74	0.88	0.17	0.43	0.41	0	1.2	1.2	0.44	0.06	0.22

* These figures include all admissions up to November, 1932.

An examination of Fig. 1 shows the compilation of data as essentially similar to that employed by Levine and Ladd.[1] In view of the fact that the hospital discontinued the statistical tabulation of the birthplaces of all admissions shortly after 1921, it has been necessary to use these authors' figures (see Fig. 1, horizontal column 2) for computing the total admissions from a given country, with the exception of the figures for negroes, who comprise slightly

over 5% of all admissions and may all be considered as American born.

Certain striking differences in incidence become apparent on closer analysis of the figures in horizontal columns 2 and 4. While 9.4% of all admissions were Russian born, only 2.8% of the pernicious anemia patients were Russian and all of these, except 1, were Hebrews. Conversely, 8.9% of all admissions were from Canada, yet 16.2% of the pernicious anemia cases were Canadian. In other words, the total admissions from both of these countries were approximately equal, 7559 Russians and 7157 Canadians, but there were only 14 Russians with the disease as compared to 81 Canadians.

Similar discrepancies may be pointed out between England and Italy. Whereas 2.9% of the total admissions were Italian born and 3.4% English, only 0.8% of the pernicious anemia patients were Italian as compared with 5% English immigrants. The same contrast is apparent between Italy and Sweden; with $2\frac{1}{2}$ times as many Italians as Swedes, there were only 4 of the former but 12 of the latter with the disease.

These differences are more strongly emphasized by reference to the last vertical column in Fig. 1 in which all admissions from foreign countries are tabulated, exclusive of those in which the disease is more prevalent, *i. e.*, United States, Canada, Ireland, England, Scotland, Sweden and Denmark. There were 14,251 (17.9%) of the total admissions from the countries not so excluded, yet only 32 (6.4%) of the pernicious anemia patients were from these countries. In contrast, 66,164 of the total admissions were from the United States, Canada, Ireland, England, Scotland, Sweden and Denmark and 465 (93%) of the pernicious anemia cases were from these countries, excluding negroes. The percentage of pernicious anemia patients from Eastern and Southern European countries is therefore 6.4% as compared with 93% from the 6 countries previously mentioned and the United States; about 14 times more prevalent in the latter group.

Fig. 2 illustrates in graphic form the data in the last horizontal column of Fig. 1, namely, the ratio of the number of patients with pernicious anemia born in a given country to the total number of admissions to the hospital for all causes from that country. The contrast here again is quite striking and it is readily seen that the majority of the patients with the disease were from Sweden, Denmark, Canada, England, Ireland and the United States, and, to a lesser extent, Scotland and Germany.

Of all the patients admitted to the hospital during the period of this survey, 0.61% had pernicious anemia, yet over 1% of all the patients from Canada, Sweden and Denmark and over 0.7% of those from Ireland and England had the disease as compared with 0.18% of those from Russia (all Hebrews except one), 0.17% from Italy, 0.06% negroes and 0.22% from miscellaneous countries.

Among the last group were 1 Lithuanian, 1 Latvian, 1 Frenchwoman, 1 Pole, 1 Portuguese, and 2 Hebrews born in Austria.

The familial factor in pernicious anemia has been definitely established (Meulengracht[21]). Moreover, it is the opinion of many that there is a definite constitutional factor involved in the hereditary aspect of this disease (Draper,[22] Cornell,[8] Barker,[23] Conner[24] and Davidson and Gulland[25]). In the light of these views, one may add the clinical impression that not only does the disease occur with greater frequency in the white races of temperate zones, but that

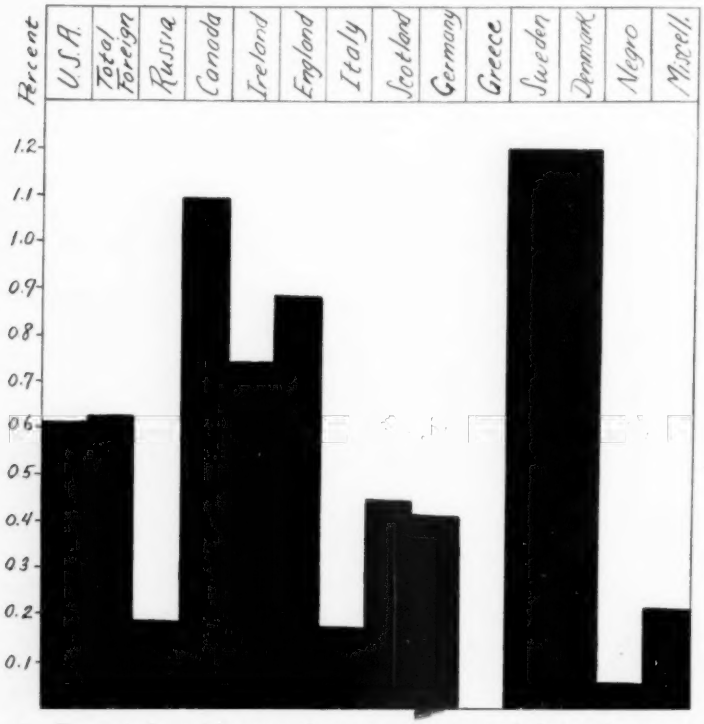

FIG. 2.—Per cent of pernicious anemia cases among total admissions from various countries.

among these people the ones affected in the vast majority of instances are the light complexioned, fair-haired type. This opinion is corroborated by Murphy[26] in a large series of patients at this clinic, and even in those cases where the disease occurred in dark-complexioned or heavily pigmented individuals, it has been possible to obtain a history of fair-complexioned ancestors or siblings in practically every case. It is of added interest to note that Erulkar[27] has remarked the occurrence of pernicious anemia in light-haired individuals in India.

The following brief résumés are recorded as striking evidence of

the importance of pigment or its absence in relation to susceptibility to the disease:

H. M. (Med. No. 36862). A young Portuguese woman, aged 24, with very dark skin, dark brown hair and gray-blue eyes gave the following family history:* Her maternal great-grandfather was exceptionally light-complexioned and although he had jet-black hair he had been considered as "one of the whitest men who had ever lived in the Azores." The maternal grandmother was 1 of 6 children, all of whom were so light-complexioned that they were known in their particular community in the Azores as the "white family." Two of the maternal grand-uncles adopted the name of "White" when they left the Azores to come to the United States, and their children, who now live in Massachusetts, bear the proper name of "White." The maternal grandmother was very fair, with light hair and blue eyes. The patient's mother, however, was quite darkly complexioned, with black hair but fair skin. There was one brother who was quite fair and had light brown hair, yet, who, as a child, was a distinct blond with golden hair. There was another brother and a sister with very dark complexions and a sister with very fair skin. These people had always considered themselves full-blooded Portuguese.

C. P. C. (Med. No. 32239). A 52-year-old Italian woman with reddish hair and brown eyes afforded the following information: Her father and mother were both born in Milan, Italy, and were fairer than the average Italian. Numerous members of the family were of the blond type and there were blond and fair-haired members on both sides. Her father and mother both had brown eyes and black hair. Of two paternal aunts one had black hair and the other blond. There were 13 siblings in the mother's family, 2 of whom had red hair. The patient stated that some of her own children "might have been taken for Swedes," 2 of her 3 sons having blue eyes and blond hair.

L. L. D. (Med. No. 38258). A 49-year-old negress stated that her mother was a white Canadian woman and that one of her brothers died at the age of 62 of a disease called pernicious anemia.

The evidence just presented is in favor of the view that the predisposition to this disease is racial in character as well as constitutional and familial. It is largely confined to those individuals endowed with a diathesis characterized by a fair complexion, light hair, blue eyes and achlorhydria. Of the 500 cases investigated there were only 66 in which the color of the irides was recorded and of these 72.7% were blue, 16.7% brown and 10.6% shades of blue. It is felt that these characteristics are definite components of the genotype in such individuals who, under the influence of certain so-called releasing factors in their environment, as yet undetermined, may eventually suffer a loss of the intrinsic factor of Castle[28] and develop pernicious anemia.

Although unrelated to the general trend of this paper, the following data are recorded as worthy of mention: Of the 500 cases studied during this survey, 274 entered this hospital over a 13-year period terminating in 1926, *i. e.*, prior to the advent of liver therapy and 226 were admitted during a period of 6 years after the advent of liver therapy. Although the absence of accurate follow-up records precludes an exact knowledge of the total mortality in both of these groups, it is definitely known that over 60% of the first

* As obtained by Dr. Marshall N. Fulton of the Peter Bent Brigham Hospital.

group are dead and very likely most, if not all, of this group have died, whereas only about 11% of the latter group have died. Definite knowledge is at hand, however, concerning 51 autopsied cases, 36 of which were performed before 1926 and 15 during the following 6 years.

The average age at death of the first group was 51 years, that of the latter 58 years; whereas the average length of life after the onset of the disease in those patients not receiving liver was 30 months, it was 29 months in the group dying after the advent of liver treatment.

The decline in the mortality due to pernicious anemia was predicted by McKinley[29] in 1929 and mortality statistics from Toronto[30] covering the period from 1923 to 1931 show a substantial lowering of the death rate due to pernicious anemia since the discovery of liver therapy. This, of course, is undoubtedly the unpublished opinion of many others. The very fact that there are so few fatalities in this group since 1926 is sufficient proof that liver therapy prolongs the lives of patients with pernicious anemia.

Observations among this series of cases concerning the causes of death in the autopsied cases indicate that those patients who received optimum liver therapy with a corresponding return of their blood to normal figures died of conditions essentially unrelated to pernicious anemia. The only possible exception to this is the type of patient who develops progressive neurologic disease in the face of adequate treatment. This has been previously intimated by Zadek[31] and Diebold[32] with regard to patients dying in spontaneous remissions and by Fahr[33] in patients dying during significant remissions following liver therapy.

In this series of 51 autopsied cases, 36 of the patients died prior to the advent of liver treatment with an average antemortem hemoglobin of 29% and 1,320,000 red blood cells per cmm. Of these, 29 died of circulatory failure and intercurrent infections as a result of the debilitating effects of anemia, 3 died of circulatory failure complicated in one instance by a chronic pachymeningitis and leptomeningitis, in another by acute hemorrhagic pachymeningitis and in the last by active tuberculosis of the hilar lymph nodes; 3 died of sepsis and another of acute tuberculous bronchopneumonia.

Fifteen patients came to autopsy after the advent of liver therapy, 10 of whom were inadequately treated as evidenced by an antemortem red cell count of 1,870,000 and hemoglobin of 39%. Six of this group died of circulatory embarrassment and intercurrent infection; in the remainder death was due to vascular accidents terminated by bronchopneumonia. The remaining 5 cases showed an average antemortem hemoglobin of 81% with an average red cell count of 4,500,000. Three of these patients died of circulatory accidents, 1 showing multiple thrombi in the pulmonary arteries and veins, another thrombosis of the right pulmonary artery and 1 thrombosis of the left coronary artery, all terminating in bron-

chopneumonia. Of the remaining 2, 1 died of a staphylococcus septicemia and 1 of carcinoma of the gall bladder with extension to the liver, and terminal bronchopneumonia.

Of the total number of cases autopsied, 10 had chronic fibrous pleurisy, not proven tuberculous; 9 showed evidence of healed, apical, non-clinical pulmonary tuberculosis, 2 had active hilar lymph-node tuberculosis and 1 died of acute tuberculous bronchopneumonia. These findings are worthy of note in the light of a recent study by Barron,[34] who believes there is a definite antagonism between pernicious anemia and tuberculosis.

Opinions have varied from time to time concerning the sizes of the liver and spleen in pernicious anemia. In this particular group, however, there was no difference in the size of the liver in those patients autopsied prior to or since the advent of liver therapy, the average weight of the liver in the whole group of 51 cases being 1598 gm. On the other hand there was an appreciable diminution in the size of the spleen in the 15 patients dying after 1926, the average weight being 171 gm. as compared with 234 gm. in the group not treated with liver. This is in accordance with the belief of some that, clinically, the spleen, in adequately treated cases, is less likely to be enlarged and possibly diminishes in size after the institution of specific therapy.

Summary. Evidence derived from a study of 500 cases of typical pernicious anemia is presented to confirm the opinion that pernicious anemia is a disease largely confined to the white race in temperate zones and that among these people there is a definite racial, as well as constitutional, predisposition, the latter being embodied in individuals endowed with a diathesis characterized by fair complexion, light hair and light-colored eyes.

An analysis of 51 cases of proven pernicious anemia, 36 autopsied prior to and 15 since the advent of liver therapy, indicates that the causes of death of those adequately treated in this latter group are not directly related to the anemia and are essentially conditions met with in ordinary people of the same age.

The weight of the spleen in patients autopsied before the advent of liver treatment was greater than in those dying after 1926, the weight being 234 gm. in the untreated group as compared with 171 gm. in the latter group. There was no change in the weight of the liver in either group, the average being 1598 gm.

The author desires to express his sincere appreciation to Dr. S. A. Levine for his many helpful suggestions and valuable criticism.

Acknowledgment is due Miss Isabel Howard for her technical assistance.

REFERENCES.

1. Levine, S. A., and Ladd, W. S.: Bull. Johns Hopkins Hosp., **32**, 254, 1921.
2. Albutt, C., and Rolleston, H. D.: A System of Medicine, Macmillan & Co., Ltd., London, 1911.
3. Bunting, C. H.: Bull. Johns Hopkins Hosp., **16**, 222, 1905.
4. Osler, W., and McCrae, T.: Modern Medicine, Lea & Febiger, Philadelphia, 1927.

5. McCann, W. S., and Maitland-Jones, A. G.: A Textbook of Medicine, Cecil, W. B. Saunders Company, Philadelphia, 1927.
6. Panton, P. N., Maitland-Jones, A. G., and Riddock, G.: Lancet, **1**, 274, 1923.
7. Montgomery, E. W.: Canadian Med. Assn. J., **85**, 1436, 1925.
8. Cornell, B. S.: Pernicious Anemia, Duke University Press, Durham, N. C., 1927.
9. Binswanger, M.: Ztschr. f. klin. Med., **105**, 249, 1927.
10. Carr, J. G.: Am. J. Med. Sci., **160**, 737, 1920.
11. Willson, C. R., and Evans, F. A.: Bull. Johns Hopkins Hosp., **85**, 1436, 1925.
12. Jamison, S. C.: South. Med. J., **19**, 583, 1926.
13. Traut, E. F.: Illinois Med. J., **51**, 322, 1927.
14. Matthews, H. O.: U. S. Vet. Bur. Med. Bull., **5**, 494, 1929.
15. Morris, H. H.: China Med. J., **43**, 768, 1929.
16. Mills, C. A.: Endocrinology, **16**, 52, 1932.
17. Yang, C. S., and Keefer, C. S.: Nat. Med. J., China, **17**, 218, 1931.
18. Williams, T. H.: China Med. J., **46**, 673, 1932.
19. Mills, C. A.: Arch. Int. Med., **46**, 741, 1930.
20. Sturgis, C. C., and Isaacs, R.: Calif. and West. Med., **39**, 73, 1933.
21. Meulengracht, E.: Am. J. Med. Sci., **169**, 177, 1925.
22. Draper, G.: Human Constitution, W. B. Saunders Company, Philadelphia, 1924.
23. Barker, L. F.: J. Am. Med. Assn., **87**, 80, 1926.
24. Conner, H. M.: Ibid., **94**, 606, 1930.
25. Davidson, L. S. P., and Gulland, G. L.: Pernicious Anemia, The C. V. Mosby Company, St. Louis, 1930.
26. Murphy, W. P.: Personal Communication.
27. Erulkar, A. S.: Clin. J., **60**, 237, 1931.
28. Castle, W. B., Townsend, W. C., and Heath, W. C.: Am. J. Med. Sci., **180**, 305, 1930.
29. McKinley, P. L.: Lancet, **2**, 1086, 1929.
30. Statistical Review of the Mortality Statistics of Pernicious Anemia in Toronto, 1923–1931, Univ. Toronto Med. J., **10**, 35, 1932.
31. Zadek, I.: Klin. Wchnschr., **8**, 1257, 1929.
32. Diebold, O.: Med. Welt, **4**, 621, 1930.
33. Fahr, T.: Deutsch. med. Wchnschr., **57**, 8, 1931.
34. Barron, M.: J. Am. Med. Assn., **100**, 1590, 1933.

OBSERVATION ON THE PRACTICAL SIGNIFICANCE OF VENOUS PRESSURE IN HEALTH AND DISEASE WITH A REVIEW OF THE LITERATURE.

By George C. Griffith, A.B., M.D.,
Visiting Physician and Director, Department of Cardiology, Presbyterian Hospital; Assistant Professor of Cardiology, Graduate School of Medicine, University of Pennsylvania,

Charles T. Chamberlain, A.B., M.D.,
Resident Physician, Graduate Hospital, University of Pennsylvania,

and

J. Roderick Kitchell, Jr., A.B., M.D.,
Resident Physician, Graduate Hospital, University of Pennsylvania, Philadelphia.

(From the Medical Department of the Graduate School of Medicine of the University of Pennsylvania.)

In a previous communication we attempted to describe a relatively inexpensive apparatus and simple technique for the determination of venous pressure according to the original direct method

of Moritz and Tabora. It is now our purpose to demonstrate its clinical application and usefulness in the hands of the general practitioner who daily is confronted in his patients with diagnostic problems in cardiovascular disease.

The literature reveals the fact that many investigators have studied the problem of venous hypertension from many angles, employed many techniques, and pointed out its significance in practically every pathologic state of the vascular system. Consequently, we realize that our subject is not a new one. On the other hand, it is our impression that most of this work has been from the standpoint of research, wherein not only hospitalization of the patients studied but also elaborate and expensive apparatus have been required. It has naturally followed, therefore, that the problems studied and the conclusions reached have been of interest only to physiologists, cardiologists and research investigators. Our experience, however, has convinced us that the information gained from venous pressure determinations in numerous disease entities can be extremely useful and interesting, not only to the internist practising in large clinics, but also to the general practitioner in the smaller communities, once his interest and curiosity are aroused, and he finds he has another simple diagnostic guide at his finger tips.

Normal Venous Pressure and Its Physiologic Variations. There are four fundamental functional factors affecting peripheral venous pressure; namely: (1) *Vis a tergo* or heart action; (2) intrathoracic pressure; (3) hydrostatic level; (4) volume of blood in the vein. Physiologic fluctuations in any one of the above is reflected in altered venous tension within its normal range.

The normal venous pressure has been reported by different authors as varying from 50 to 150 mm. of water. In Table 1 are listed the normal ranges as determined by various investigators:

TABLE 1.—NORMAL RANGES OF VENOUS PRESSURE.

	Water. mm.		Water. mm.
Moritz and Tabora[1] (1910)	100	Gonczy, Kiss and Enyedy[5]	120
Schott[2] (1912)	130	Criep[6]	102
Villaret, St. Girons and Jacquemin-Guillaume[3]	130	Eyster and Middleton[7]	110
Bedford and Wright[4]	50–150	Conradi[8]	80–130

Needless to say, the fact that different techniques have been used will necessarily account for some of the apparent discrepancies in the normals arrived at by different investigators. Based on our own and the findings of others, we have accepted a range of 60 to 120 mm. of water as normal for subjects at rest in the supine position; readings above 140 and below 40 we believe are always pathologic.

According to Criep[6] there is an increase in venous pressure with age up to 35 years, and then a decrease to 50. This increase and decline remains within normal limits, however.

Venous pressure rises with exercise,[4] and during exercise there is

a slight secondary fall as increased cardiac output results from increased venous load.[9] For this reason patients should be at rest for some time (at least 15 minutes) before a reading is taken.

No definite relationship has been found to exist between arterial and venous pressure according to our observations. Bedford and Wright[4] came to the same conclusions, and Criep,[6] while stating that there is a general tendency for venous pressure to drop as systolic pressure rises above 115 and to rise with diastolic pressure, finally decides that no constant relation can be determined.

We have found that the pressure in the femoral vein, with the patient at rest in the supine position is usually from 10 to 40 mm. higher than pressure in the arm veins of the same patient—perhaps due to mechanical pressure effects within the abdomen. We are not inclined to attach much importance to this difference unless the pressure in the femoral exceeds 140 mm.

Evans[10] states that obesity raises the venous pressure due to pressure on the veins by fatty tissue. Conversely, emaciation lowers venous pressure.

Venous Pressure in Cardiac Decompensation. I. Diagnosis.—It is accepted that the output of the heart is determined by the venous load put upon it. An increase in the load on the normal heart up to a point results in an increased output. Cardiac failure is defined by Eyster[11] as "that condition in which the venous pressure exceeds the range within which the heart is capable of responding, by increased work, to increased venous load." This increase in load, with failure, can occur in either the right or the left heart or both. We are able to measure the load on the right heart, but at present no means is available for measurement of the intrapulmonic pressure, which determine the load on the left heart.[2]

A distinction should be drawn here between right and left sided heart failure. Clinically the usual types of decompensation involve the right heart alone or a combination of the right and left hearts. Here the venous pressure is raised in the greater circulation, and can be measured quantitatively. Rarely one meets with cases of cardiac failure involving only the left heart. Here the venous pressure is raised in the lesser circulation (where we are unable to measure it) and the venous pressure in the greater circulation is not affected until the right heart also gives way. Any further reference hereafter to cardiac failure will mean failure including the right heart.

In *cardiac failure*, whether of primary or secondary origin, venous pressure is always elevated.[6, 7, 10, 17] Furthermore, such venous hypertension antedates the clinical signs and symptoms of failure by several hours, at least.[11, 16, 18] In view of these facts it will be seen that venous pressure readings in cases of suspected or impending heart failure may well prove a valuable therapeutic and diagnostic aid to the clinician.

In *pneumonia*, where the usual signs of congestive failure are difficult to recognize because they are obscured by the signs of respiratory embarrassment, venous pressure readings are of extreme value. In fact, Kastlin and Maclachlan[16] state that venous pressure, rather than the classic arterial tension, is the delicate prognostic and diagnostic criterion in pneumonia when the state of the circulatory system is the crux of the situation. Cardiac failure can invariably be positively diagnosed, if present, in the course of pneumonias when venous pressure readings are made routinely.

Venous pressure has also been of value in *differential diagnosis*. As there is no rise in this pressure in cases of allergic asthma, pneumoconiosis, emphysema and chronic pulmonary fibrosis, we have a valuable aid in differentiating the dyspnea and cyanosis due to these conditions from that caused by acute right heart failure.[10] In cardiac decompensation, the venous tension usually varies from 140 to 300 mm. of water, with values of 160 and upward in cases of acute failure. The pulmonary conditions named above usually show pressures from 60 to 120 mm., while allergic asthma cases often show pressures at the upper limits of normal, probably due to increase of intrathoracic pressure caused by increased expiratory effort.

In several cases of acute heart failure and of allergic asthma admitted as medical emergencies, immediate venous pressure determinations proved to be of tremendous value for us in differentiating the two conditions. In one instance the patient had received several 1 cc. injections of adrenalin outside, in a fruitless attempt to alleviate the symptoms. A venous pressure reading showed a hypertension of 240 mm. of saline, and venesection proved effective.

In cases of *pneumothorax*, unless enough collapse of lung tissue is present to cause dyspnea, no change in the venous pressure is found.[10] Similarly, in a case of bilateral pneumococcic *empyema* which we observed, the venous pressure remained normal throughout.

In *cerebral-vascular accidents* complicated by cardiac failure, the decompensation is at times overlooked because of the confusing chest signs which may be present. Such cases are more intelligently treated when the decompensation is recognized early by venous pressure determinations.

II. Prognosis. In the prognosis of cardiac failure, venous pressure determinations are valuable as to the degree and progress of the condition not obtainable by other means. Clark[12] was the first to set 200 mm. of water as the critical level in heart failure: above this level a further rise has unfavorable prognostic significance; a fall from this level lends a favorable outlook. Others have agreed with Clark.[12]

In pneumonia and other acute conditions in which cardiac failure may occur, the venous pressure readings—useful in diagnosis—

become doubly useful when prognosis is considered, since it is upon the sufficiency of the circulatory system that the final outcome often depends. Kastlin and Maclachlan[16] have shown that a persistently elevated venous pressure with a pulse rate above 120 usually foretells a fatal outcome. A low venous tension with a pulse below 120 makes for a good prognosis. In several of their cases, terminating fatally, arterial pressure remained normal during the course of the disease.

III. Treatment. Venous pressure readings in decompensated patients during therapy calculated to restore compensation will show, in cases reacting favorably to such treatment, a progressive return of venous pressure to normal.[7, 10, 11, 12, 17, 19] This level will be maintained as long as compensation lasts. Consequently it has been found practical to use venous pressure as an index to the efficacy of the treatment. During digitalization, readings are taken in a series spaced at 2- or 3-day intervals. After compensation is restored the intervals may be increased to weeks or months, as long as the patient is under observation. By this method it is relatively simple to detect early a beginning relapse into the decompensated state, the venous pressure elevation in cardiac failure occurring as mentioned above, before the clinical signs and symptoms become definite. Treatment may then be instituted at once and the heart muscle spared as much as possible.

Concerning venesection, the obvious step in right heart failure, from a theoretical standpoint, is artificially to remove some of the venous load on the heart by blood-letting. Unfortunately, in the past, this measure has generally been used as a procedure of last resort, more conservative treatment having failed. Such cases going on to a fatal outcome, venesection has been looked on with distrust if not with actual disapproval.[16]

Clark, in 1915, was the first to champion venesection when venous pressure rose above a critical level of 200 mm. of water. Recently other investigators have concurred in emphasizing the rationale of such a procedure and in deploring the fact that venesection is employed only in desperate cases where obviously any treatment would fail.[6, 14, 16] At a level of 200 mm. the patient is usually still in such condition that lost compensation, which digitalis and rest alone may not restore, will still respond favorably to the more radical procedure of venesection. This should be done in cases where the venous pressure is rising above the critical level, or remaining high, in spite of conservative treatment. In such cases at least 500 cc. or more of blood should be removed, as Meek and Eyster[20] have shown that at least this amount is required if any benefit is to be expected. Venous pressure readings are an index in these cases to the degree of immediate relief afforded the patient and, when taken in series, give information as to the duration of such relief.[14]

IV. Venous Pressure Elevation Due to Localized Obstruction. There are only two conditions causing venous pressure elevation: heart failure and obstruction to venous return. In the majority of cases of elevated venous pressure from local block, readings in different extremities will usually locate the obstruction. In one type, however, this does not hold true. Constrictive pericarditis, or *concretio cordis*, raises the general venous pressure at times regardless of whether it is postinfectious or idiopathic in origin. Many signs and symptoms are common to this condition and to cardiac failure, but the causative mechanisms are different. The essential defect in constrictive pericarditis is a limitation of diastolic relaxation of the heart caused by encircling bands of scar tissue, resulting in a low fixed stroke output of the heart. An excellent review of this condition is given by Burwell and Strayhorn.[21] In a case reported by these authors the venous tension reached 240 mm. and Volhard and Schmieden[22] report pressures up to 300 mm. In the 2 cases we have studied the pressures reached 240 and 265 mm. respectively. These pressures varied somewhat in different extremities and were of use in locating for the surgeon the main adhesive bands.

Although venous pressure readings are of diagnostic service in these cases, their greatest use is in evaluating the postoperative results of surgical release of constricting bands and adhesions. In our 2 cases referred to above, the venous pressures fell from 265 to 120 mm. in 1 case, and from 240 to 170 in the other, after surgery.

Evans[10] states that edema raises the venous pressure. As this occurs only in the part involved, readings in different extremities are of value in differentiating cardiac, renal and inflammatory edema. We have had no direct experience with this.

Evans also states that with ascites high venous pressures obtain in the legs. These return to normal with paracentesis. This we have found to be true in a certain group of cases where ascites is caused by portal vein block, as in portal cirrhosis. In 2 other cases studied we found ascites with elevated femoral pressure. Venous tension in the arm veins was normal or low. Paracentesis in each patient removed 4000 cc. of ascitic fluid, but the venous pressure in the femoral veins did not drop to normal. In 1 case it fell from 245 to 185 mm. and in the other from 225 to 170 mm. Further study, including exploratory laparotomy, revealed extensive peritoneal disease with many adhesions and enlargement of the mesenteric glands. In a 3d case, with elevation of femoral venous pressure and with evidence on physical examination of ascites, numerous attempts at paracentesis failed, presumably because of adhesions with loculation of fluid. Laparotomy here also revealed chronic peritoneal disease.

We have seen no reference in the literature to date regarding cases similar to the last three mentioned. While such a series is obviously too small for any conclusions, we believe the observations are worthy of further study and consideration.

V. Venous Hypotension. Search of the literature fails to reveal any reference to the pathologic significance of persistent venous hypotension. In the course of our investigations we have encountered several cases with such findings. A series of venous pressures taken over a period of time showed the venous pressure rising as the patients improved clinically. One such case was diagnosed carcinoma of the esophagus with cachexia and dehydration. The venous pressure was 20 mm. of water. One month after gastrostomy with regular feedings the venous pressure rose to 60 mm. (*i. e.*, normal). Another case of extrinsic carcinoma of the larynx with emaciation showed a venous tension of 10 mm. Both the clinical condition and the venous tension in this patient have remained unchanged.

A venous pressure reading on a case of acute coronary accident in the emergency ward revealed a pressure of only 5 mm. of water. The patient was confined to bed in the hospital over a period of 2 months. As he slowly convalesced, his venous pressure rose. At the time of discharge the venous tension was 94 mm. A similar case of acute vascular accident was observed in a patient who suffered a pulmonary embolus after appendectomy. The day following this accident the venous pressure was 40 mm. Over a period of 2 weeks his venous tension rose to 120 mm.

The above illustrations of venous hypotension are mentioned purely as suggestive; our observations are as yet too limited to serve as the basis for any conclusions. Possibly the cause for venous pressure in cachexia is in reduced blood volume and in reduced pressure on the venous channels.[10, 17] We have no explanation to offer for a fall in peripheral venous pressure in the acute vascular accidents, except the possibility of splanchnic shock, increasing the amount of blood in the splanchnic area at the expense of the peripheral circulation or of a lowered *vis a tergo* from the weakened myocardium, reducing pressure in the venous channels.

In regard to the meager literature on venous hypotension, it is interesting to note that Bedford and Wright[4] state that with the direct method of Claudé, which they used, it was difficult to measure accurately low venous pressure. Although we have had no experience with the indirect method it is possible the same criticism applies to it. With our apparatus, low venous tensions are as readily measured as higher pressures. It is to be hoped that the significance of venous hypotension will be more thoroughly investigated.

Summary and Conclusions. 1. With a simplified apparatus and technique at his command the general practitioner should find accurate venous pressure determination a practical diagnostic, prognostic and therapeutic guide in primary congestive heart failure and in other disease entities complicated by or simulating cardiac decompensation.

2. The use of venous pressure in various clinical conditions is herein discussed, with examples from our own experience.

3. The significance of venous hypotension has yet to be adequately investigated and furnishes another fruitful field for clinical research.

REFERENCES.

1. Moritz, F., and v. Tabora, D.: Deutsch. Arch. f. klin. Med., **98**, 475, 1910.
2. Schott, E.: Ibid., **108**, 537, 1912.
3. Villaret, M. S., Girons, F., and Jacquemin-Guillaume, G.: Compt. rend. Soc. de biol., **84**, 80, 1921.
4. Bedford, D. E., and Wright, S.: Lancet, **2**, 106, 1924.
5. v. Gonczy, V. I., Kiss, J., and Enyedy, Z.: Ztschr. f. d. exp. Med., **70**, 236, 1930.
6. Criep, L. H.: Med. Bull. Vet. Admin., **8**, 463, 1932.
7. Eyster, J. A. E., and Middleton, W. S.: Arch. Int. Med., **34**, 228, 1924.
8. Conradi, A.: Policlinico (sez. med.), **30**, 573, 1923.
9. White, H. L., Barker, P. S., and Allen, D. S.: Am. Heart J., **1**, 160, 1926.
10. Evans, W.: New England J. Med., **207**, 934, 1932.
11. Eyster, J. A. E.: J. Am. Med. Assn., **97**, 1269, 1931.
12. Clark, A. H.: Arch. Int. Med., **16**, 587, 1915.
13. Foley, E. F.: Med. Clin. North America, **12**, 153, 1928.
14. Eyster, J. A. E., and Middleton, W. S.: Am. J. Med. Sci., **174**, 486, 1927.
15. Hooker, D. R.: Am. J. Physiol., **35**, 73, 1914; **40**, 43, 1916.
16. Kastlin, G. J., and Maclachlan, W. W. G.: Arch. Int. Med., **4**, 959, 1931.
17. Hooker, D. R., and Eyster, J. A. E.: Bull. Johns Hopkins Hosp., **19**, 274, 1909.
18. Villaret, M., St. Girons, F., and Grellety-Bosviel, L.: Bull. et mém. de Soc. méd. de hôp. de Paris, **45**, 847, 1921.
19. Blumbard, H. L., and Weiss, S.: J. Clin. Invest., **5**, 379, 1928.
20. Meek, W. S., and Eyster, J. A. E.: Am. J. Physiol., **1**, 56, 1921.
21. Burwell, C. S., and Strayhorn, W. D.: Arch. Surg., **24**, 106, 1932.
22. Volhard and Schmeiden: Klin. Wchnschr., **2**, 5, 1923.

ARTERIOVENOUS FISTULA INVOLVING THE COMMON FEMORAL ARTERY IDENTIFIED BY ARTERIOGRAPHY.

By Bayard T. Horton, M.D.,

M.S. IN MEDICINE, F.A.C.P.

ASSOCIATE IN SECTION IN DIVISION OF MEDICINE, THE MAYO CLINIC; INSTRUCTOR IN MEDICINE, THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH, GRADUATE SCHOOL, UNIVERSITY OF MINNESOTA.

The reasons for reporting this case are to illustrate the importance of definitely determining the site of an arteriovenous fistula by means of arteriography, and to demonstrate the clinical signs and symptoms of acquired arteriovenous fistula. This appears to be the first time arteriography has been used here in this type of case, and I had not seen similar reports in the literature at the time this case was originally reported.[1] Yater,[2] also, has referred to my original report as the first of its kind.

Report of Case. A youth, aged 19, was admitted to the clinic October 31, 1931, with bird shot wounds in both thighs. One shot had penetrated the upper third of the right thigh over the great vessels and painless swelling had followed immediately. Another shot had entered the anterior part

of the left thigh in the lower side, but had not caused swelling, or other symptoms (Fig. 1). Roentgenograms revealed 1 small shot in each thigh. Pulsations in the right femoral, right popliteal, right posterior tibial and right dorsalis pedis arteries were normal at the time of examination, and no bruit could be detected over the right thigh.

A compression bandage was applied over the swollen region of the right thigh. The patient was in the hospital under observation for 4 days, and during that time the swelling in the thigh gradually subsided. On the 6th day after the injury, a slight bruit could be heard over the femoral artery at the point where the shot had entered; at times the bruit was absent. A well-developed bruit, with thrill, was present 24 days after the injury over the upper third of the right thigh. The bruit was heard throughout

FIG. 1.—The points of entrance of the bird shot, 29 days after the injury. Enlargement of the lateral aspect of the right thigh is evident.

the cardiac cycle and was accentuated with each beat of the heart. When the right femoral artery was closed by digital pressure below the inguinal ligament, the apex beat of the heart decreased from 10 to 12 beats per minute

November 24, determinations of oxygen content were made on blood removed from superficial veins of the right and left arms, right femoral vein, left femoral vein, and right femoral artery. The blood in each instance was withdrawn under oil without the use of a tourniquet, and the determinations of oxygen were made by the van Slyke gasometric method. The patient had been lying in a horizontal position for about 30 min. before the specimens of blood were withdrawn. The oxygen saturation of blood from the right arm vein was 57.2% by volume; from the left arm vein, 46.7; from the left femoral vein, 76.6; from the right femoral vein, 85.5, and from

the right femoral artery, 93.8%. Blood from the right femoral vein was bright red and was practically the same color as that from the right femoral artery. Blood from the left femoral vein was darker and corresponded more closely to the color of the blood removed from the arm veins than to that of blood from right femoral artery. Blood counts, urinalysis and the serologic test for syphilis gave negative results. Clinically, it was apparent that this patient had an arteriovenous fistula in the right thigh, probably involving one of the small branches of the femoral artery rather than the femoral artery itself.

July 8, 1932, an arteriogram of the right femoral artery was made by injecting into it 25 cc. of thorotrast. At the time the injection was made,

FIG. 2.—Arteriovenous fistula between femoral artery and vein; *a*, bird shot; *b*, femoral artery; *c*, femoral vein; *d*, saccular enlargements in the femoral vein.

the right femoral artery was closed by digital pressure just proximal to the site of injection. A series of films was made as quickly as possible. The patient experienced no ill effects from the procedure. The arteriogram revealed evidence of an abnormal communication between the femoral artery and vein (Fig. 2). The femoral vein was well outlined, indicating that the opaque medium had leaked from the artery into the vein by way of the fistula.

The patient was examined again March 24, 1933. The right thigh had become definitely larger than the left, a loud bruit could be heard over the entire thigh, and there was a marked thrill in the middle and upper thirds. The superficial veins were increased in size and number, as compared with

those of the normal left thigh. With the patient horizontal, the blood pressure of the left and right arms was 120 mm. Hg systolic and 70 diastolic, of the left thigh 120 systolic and 80 diastolic, and of the right thigh 140 systolic and 100 diastolic. When the right femoral artery was compressed just below the inguinal ligament, the apex beat of the heart dropped from 80 to 66 beats per minute. After the patient had been at rest for 20 min., the rate of the heart at the apex was 68 beats per minute. It dropped to 54 beats per minute when the right femoral artery was again closed by digital pressure. In a roentgenogram of the thorax the heart appeared to be of normal size. The cardiac output, as determined by the Grollman method, was 3.9 liters per sq.m. of body surface. This indicates a definite increase over the normal.

This case illustrates the importance of arteriography in determining the site of abnormal arteriovenous communications. With the history, the presence of a bruit and thrill over the right thigh and the bradycardiac reaction, the diagnosis of arteriovenous fistula of the acquired type seemed definitely established. The diagnosis was confirmed by the demonstration of a high admixture of arterial and venous blood in the right femoral vein. The site of the fistula could be determined only by means of arteriography, or by surgical exploration.

BIBLIOGRAPHY.

1. Horton, B. T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography, Proc. Staff Meetings, Mayo Clinic, **8**, 189, 1933.

2. Yater, W. M., and White, C. S.: Roentgenographic Demonstration of an Arteriovenous Aneurysm by Means of Thorotrast, Am. J. Med. Sci., **186**, 493, 1933.

THE SYNDROME OF OBSTRUCTION IN THE LESSER CIRCULATION.*

By James J. Waring, M.D.,
PROFESSOR OF MEDICINE,

AND

W. C. Black, M.D.,
ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF COLORADO, SCHOOL OF MEDICINE, DENVER, COLO.

(From the Department of Medicine and Department of Pathology, University of Colorado, School of Medicine.)

In this paper it is proposed to discuss a group of conditions which have in common the clinical features of cyanosis, dyspnea, polycythemia and right ventricular hypertrophy due to prolonged obstruction in the lesser circulation.

The oxygenating apparatus of the animal organism consists of an alveolocapillary wall set in between two distributing systems;

* Read May 9, 1933, at the Annual Meeting of the American Climatological and Clinical Association, Washington, D. C.

on one side is the air with its life-sustaining oxygen, the necessary airways and respiratory pump of the suction type, and on the other is the blood with the oxygen-carrier hemoglobin, a distributing system of bloodvessels and the circulatory force pump, the heart. If one considers only the steps in the process of oxygenation, it will be noted that the respiratory system has but one responsibility, that of delivering to the necessary respiratory surface area oxygen in sufficient quantity and at adequate pressure to meet the demands of the organism. The circulatory pump, however, has two responsibilities. It must deliver to the opposite side of the alveolocapillary wall hemoglobin for the loading of oxygen, and then it must transport that oxygen and discharge it at the proper unloading stations throughout the body. Oxygenation is completed by the delivery of active oxygen to the cell. Anoxemia may be the result of a defect at any point in this apparatus, from the atmospheric reservoir of oxygen to the final unloading station at the level of the cell. At one extreme stands mountain sickness, at the other cyanid poisoning, in between are the various pulmonary and arterial conditions in which acute or chronic anoxemia of greater or less severity may be found. In Fig. 1 are shown the chief points at which obstruction in the "lesser circulation" may occur.

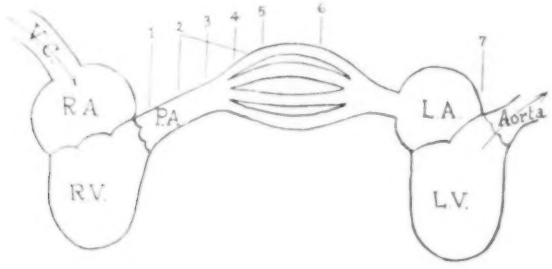

FIG. 1.—Diagram of lesser circulation showing most common causes of obstruction and their locations.

Obstructive lesions of the lesser circulation.

1. Congenital heart disease.
2. Pulmonary thrombosis and embolism.
3. Pulmonary arterial disease
4. Pulmonary arteriolar lesions
   - Arteriosclerosis.
   - Arteriolosclerosis.
   - Inflammatory
     - Syphilis.
     - Rheumatic fever.
     - Thromboangiitis.
5. Reduction of capillary bed.
   - Emphysema.
   - Pulmonary neoplasms.
   - Pulmonary tuberculosis.
   - Pneumoconiosis, etc.
6. Venous thrombosis.
7. Mitral stenosis.

The subatmospheric pressure in the chest not only keeps the pulmonary peripheral pressure low (the pressure in the pulmonary artery is only 20 mm. Hg), but assists the respiratory and circulatory functions of absorption, transportation and elimination of gases by its expansile effect upon the vascular bed and by its aspirating effect upon the blood. The anatomic evidences of this low pulmonary peripheral resistance are found on the one hand in the relatively small amount of muscle tissue normally present in the walls of the pulmonary arterioles, and on the other hand in the thinness of the right ventricle, normally 3 to 4 mm., as compared with a thickness of 12.5 mm. for the left ventricle, which works against a much higher peripheral resistance.

The primary effect of obstruction in the lesser circulation is to increase the blood pressure in the pulmonary artery; secondary effects are to produce anatomic changes in the pulmonary artery (arteriosclerosis) and in the right ventricle (hypertrophy). Secondary vascular changes may add to the obstructive effects of the primary lesion. The effect upon respiratory function is dependent upon the location, magnitude and *tempo* of the obstruction.

Because the pulmonary vein is remarkably free from disease, the only point beyond the capillaries at which obstruction is commonly found is at the mitral valve. The frequent association of pulmonary arteriosclerosis with mitral stenosis is generally ascribed to the heightened pulmonary arterial pressure. Since the primary obstruction at the mitral valve is beyond the pulmonary capillaries, the effect upon oxygenation is slight, until compensation fails.

The conditions in which we are particularly interested are those in which obstruction may be found anywhere from the right ventricle out to and including the pulmonary capillaries. Discussion will pursue the following plan:

I. Congenital cardiac defects of the cyanotic type.
II. Pulmonary thrombosis and embolism.
  A. Experimental pulmonary thrombosis and embolism.
    1. Partial occlusion of pulmonary veins.
    2. (*a*) Ligation of a main branch of the pulmonary artery.
      (*b*) Ligation of the main trunk of the pulmonary artery.
    3. Pulmonary embolism.
  B. Clinical illustrations of pulmonary thrombosis and embolism.
III. Sclerotic and inflammatory lesions of the small arteries and arterioles.
IV. Processes which affect primarily the capillary bed.

I. Congenital Cardiac Defects of the Cyanotic Type. The frequency of dyspnea, cyanosis, polycythemia and right ventricular hyper-

trophy in congenital cardiac defects in which there is a venous arterial shunt is too well known to justify extended discussion here. We confine ourselves to emphasizing the fact that precordial pain and syncope, two important symptoms common in congenital cardiac defects of the cyanotic type, were noted also in MacCallum's case of obliterative arteriolosclerosis and in Frothingham's case of extensive bilateral thrombosis of the small branches of the pulmonary arteries.

II. Pulmonary Thrombosis and Embolism. *A. Experimental Pulmonary Thrombosis and Embolism.* Obstruction of the lesser circulation has been produced experimentally in three different ways (Dunn,[1] Underhill,[2] Mann,[3] Binger *et al.*,[4] Schlaepfer,[5] Haggart and Walker[6]): (1) By ligation of a main branch of the pulmonary vein; (2) by partial or total constriction of the pulmonary artery itself; (3) by the embolic occlusion of smaller or larger branches of the pulmonary artery by the intravenous injection of paraffin, suspensions of potato starch or seeds of various sizes.

1. *Partial Occlusion of the Pulmonary Veins of One Lung.* This causes a prompt and a greater rise in pulmonary arterial pressure than when the pulmonary artery is partially ligated (Haggart and Walker[6]). At first the lung on the obstructed side shows great stasis and many hemorrhages in the alveoli. This exudate is slowly absorbed and replaced by a proliferation of connective tissue along the capillaries within the alveolar walls. After a year the fibrosis is well marked around the alveolar capillaries and around the medium-sized branches of the pulmonary artery (Schlaepfer[5]). In contrast, the lung on the unobstructed side shows early a physiologic and later a compensatory emphysema, but no connective-tissue proliferation in the alveolar walls. After a year the circumference of the pulmonary artery of the side not subjected to operation is larger than that of the other side.

2. *(a) Ligation of a Main Branch of the Pulmonary Artery.* Sauerbruch and Bruns[8] found experimentally that if a main branch of the pulmonary artery was ligated, fibrosis and shrinkage of the lung followed. In other words, a functionless lung is the result of sudden complete interference with its circulation. How much of the pulmonary arterial circulation may be cut off without anoxemia, the interrupted blood flow being detoured through other pulmonary channels along with the blood normally traversing them, we do not know. Much depends upon the condition of the myocardium and the state of the other lung. Experimentally, Haggart and Walker[6] found that clamping the left branch of the pulmonary artery for a period of time measured in minutes caused an immediate average, often only temporary, rise in pulmonary pressure of about 29 per cent, but that such a procedure brought about no significant variation in the size of the heart, heart rate or heart output. From 52 to 66 per cent of the pulmonary circulation could be cut off

without significant variation in the general circulatory condition of the animal. A critical point, however, was reached beyond which a circulatory collapse was precipitated by even a minute increase in the arterial obstruction. Dunn,[1] Binger[4] and others have found in experimental embolism a critical point of the same nature.

The results of these investigations may be summarized: Interference with respiratory function by grades of obstruction in the lesser circulation, comparable to what is often seen clinically, is easily demonstrable experimentally, but on account of great technical difficulties and the brief period of time that obstruction is applied in experiments on resting animals, the same cannot be said for the effects upon pulmonary arterial pressure and the right side of the heart. However, the clinical and pathologic evidences of heightened pressure and increased burden on the right ventricle are unmistakable.

(*b*) *Ligation of the Main Trunk of the Pulmonary Artery.* The pulmonary arterial pressure rises at once to an amount from 121 to 267 per cent of its previous level and then falls as the animal dies. The general systemic blood pressure falls sharply to one-third of the control level, the heart dilates, the minute volume shows a dimunition of from 15 to 77 per cent and respiration becomes irregular and then stops.[6]

3. *Pulmonary Embolism.* Binger, Brow and Branch[4] say that the gross and microscopic pathology of lungs subjected to pulmonary embolism by the intravenous injection of starch suspensions is characterized by evidences of congestion, edema and atelectasis. These changes are associated with a reduction in lung volume, a decreased elasticity of the pulmonary parenchyma and a shallow tidal air. In 4 experiments on dogs they found the average arterial oxygen saturation before embolism 89.2 per cent and after embolism, 71.6 per cent. Following "seed" embolism, in which larger vessels are obstructed, these workers found a more marked arterial anoxemia than in "starch" embolism. In 12 dogs the average arterial oxygen saturation was 87.56 per cent before embolism and 62.68 per cent after embolism.

Binger, Brow and Branch[4] attribute the anoxemia of experimental pulmonary embolism to a "change in the quantitative relation of blood flow to the vascular diffusion area in the lungs. The nature of this changed relationship is twofold: (*a*) An increased rate of flow through the capillaries, the flow being so rapid that the blood cannot assume its normal load of oxygen; (*b*) a compensatory dilatation in the capillaries which are crowded with corpuscles in columns so thick as to interfere with the normal inward diffusion of oxygen."

Finally, as Dunn says, the results of all these investigations on obstruction in the lesser circulation must be weighed in the light of the knowledge that they were performed upon the "resting animal."

B. Clinical Illustrations of Pulmonary Thrombosis and Embolism. Multiple thrombosis of the smaller branches of the pulmonary artery is not uncommon, but occlusion of a main branch is rare, and it is even more rare for the victim to survive long enough to show a secondary polycythemia from the effect of anoxemia on the bone marrow, and right ventricular hypertrophy from the prolonged effect of the increased burden on this side of the heart. Means and Mallory[10] have reported a case of this type. Their patient, a man, aged 60 years, showed marked dyspnea, cyanosis and swelling of the ankles. At a single examination the red cell count was not increased. On physical examination the lungs were notably clear. Congestive heart failure was the chief cause of death. At the postmortem examination both ventricles were much hypertrophied and dilated. The right ventricular wall was 7 mm. in thickness. The most important lesion, however, was complete thrombotic occlusion of the right pulmonary artery. "The pulmonary arteries beyond the point of thrombosis were entirely normal in appearance until the peripheral portion of the lung was reached, where many were found partially or completely occluded by fibrous plugs, typical in appearance of completely organized thrombi. Many of these showed canalization. It is particularly interesting that exactly similar lesions were found in peripheral portions of the left lung." The degree of organization of the clot suggested that it had been present for weeks, possibly months. A well-developed compensatory circulation through the bronchial artery and two other vessels which apparently originated from the inferior thyroid artery furnished additional evidence of the age of the obstruction. The reducing effect of the arterial occlusion upon the capillary bed is evidenced by the fact that the capillaries of the alveolar walls were difficult to make out, and very few red blood cells were found in the septa. Means and Mallory conclude with the statement that cyanosis and right-sided heart failure without other obvious cause may suggest the presence of this lesion. In his paper on "Pulmonary Arteriosclerosis," Ulrich[11] expresses much the same thought when he says: "By the simple expedient of finding no, or very little, evidence of congestive failure at the base of the lungs, when clinically there is a large liver, evidence of ascites and edema, the diagnosis of primary pulmonary sclerosis can be established." It would be more conservative to say that the syndrome of failure or abnormal strain of the right side of the heart without other obvious cause indicates obstruction in the lesser circulation, the exact cause of which must be otherwise determined.

Barnes and Yater[12] report a case of a man, aged 34 years, who died from failure of the right ventricle due to ancient thrombus in the pulmonary arteries. This man had two severe attacks of pain in the chest with intense dyspnea, apparently signaling the arrival of emboli in the lungs. He also had cyanosis, polycythemia, peripheral

edema and bilateral hydrothorax. At the postmortem examination, fairly well-organized thrombi were found in the pulmonary arteries between the main trunk and the subdivisions into their smaller branches. The right ventricle was much hypertrophied and the pulmonary artery much dilated.

A patient of Jump and Baumann,[13] with pulmonary thrombosis showed marked cyanosis, dyspnea, moderate edema and died shortly with signs of failure of the right heart. He lived long enough, however, to develop a fairly high-grade secondary polycythemia of 7,700,000 and marked right ventricular hypertrophy. The valves were all normal. Both main branches of the pulmonary artery were nearly filled with adherent thrombotic material. Jump and Baumann say: "Mechanically, the thrombus resembles the obstruction seen in congenital stenosis of the pulmonary artery. This obstruction puts additional weight on the right side of the heart, and hypertrophy follows. The cyanosis occurs because of slowing of the blood flow, and anoxemia comes from a greater utilization of oxygen by the tissues."

Since the only communication between the bronchial artery and the pulmonary arterial system is by way of the pulmonary capillaries, and not by way of vascular connections of respectable size, it is very unlikely that a collateral circulation in the lungs can be developed through the bronchial artery to compensate for obstruction in the main branches of the pulmonary artery, at least so far as respiratory function is concerned. Moreover, since the bronchial artery carries arterial blood, it is a little difficult, anyhow, to see what assistance in the business of oxygenation a circulation through it could furnish. In the absence of an adequate collateral circulation a reduction in the capillary bed must necessarily be accompanied by a reduction in effective respiratory surface area. We feel, therefore, that whether obstruction be in the main branches of the pulmonary artery or in the arterioles, anoxemia is due in great measure to inadequate re-oxygenation in the lungs.

III. Sclerotic and Inflammatory Lesions of the Small Arteries and Arterioles. Usually two forms of pulmonary arteriosclerosis are described: (1) Primary, and (2) secondary. The primary form is rare, of obscure etiology, and affects chiefly the small arteries, arterioles and capillaries. The larger vessels may or may not be involved. It has been called arteriolocapillary fibrosis of the lung and compared to the similar condition in the kidney. Moschcowitz,[14] who relates all pulmonary arteriosclerosis to increased pulmonary arterial pressure and doubts the existence of a primary form, says: "The resemblance between lesions of the pulmonary capillaries in hypertension of the lesser circulation and those of the glomerular capillaries in essential hypertension is striking, and in almost every respect they are identical." It produces a narrowing, even oblitera-

tion of the small vessels of the lung, which results on the one hand in serious interference with respiratory function and on the other in adding to the burden of the right heart by increasing pulmonary arterial pressure. In this paper our interest is not so much in the etiology of the condition as in its effects upon respiratory function.

The secondary form is more common, involves the larger arteries and is apparently ascribable to the increase in pulmonary arterial pressure from down-stream changes in the heart and lungs (mitral stenosis, emphysema, pulmonary fibrosis). It may be associated with a generalized arteriosclerosis. As Pund and Phinizy[15] put it, these changes are usually without clinical significance or are overshadowed by symptoms produced by the primary disorder.

Moschowitz says that the difference between arteriosclerosis of the pulmonary circulation and that of the major system is solely one of intensity of the process. He thinks alveolar capillary lesions are pathognomonic of hypertension of the lesser circulation and its consequent arteriosclerosis, and that the thickening and hyalinization of the alveolar capillary wall embarrasses gas exchange and produces anoxemia. Increase of pericapillary connective tissue, which may reach the proportions of a true interstitial infiltration, is the result of a progressive interference with the blood supply.

Three cases (1 of Frothingham,[16] 1 of MacCallum[17] and 1 of our own) are now summarized to illustrate the effects of obstruction in the smaller pulmonary vessels upon oxygenation and the right ventricle. Frothingham reported a case of extensive bilateral progressive thrombosis of the smaller branches of the pulmonary arteries in a woman, aged 38 years, whose chief complaint was increasing shortness of breath. Severe pains under the left breast and a tendency to syncope were symptoms that remind us of similar attacks in the cyanotic group of congenital cardiac defects and were probably due to the same cause, namely, anoxemia. Cyanosis on slight exertion was marked, the red cell count was slightly increased, the electrocardiogram indicated right ventricular preponderance, the Wassermann reaction was negative and the vital capacity was 53 per cent of normal. She became gradually more cyanotic and short of breath even at rest, and finally died struggling for breath. "One of the attending physicians remarked that had the symptoms developed suddenly it would be the typical picture of an embolus in the pulmonary artery." At the postmortem examination, Frothingham found an extensive thrombosis which began in the smallest branches of the pulmonary artery and propagated centripetally toward the larger branches. Practically all pulmonary arterial branches of the third and fourth orders were completely occluded by thrombi which varied in size from pinhead-sized masses firmly attached to the vessel wall to similar appearing masses, 1 or 2 cm. in length, and filling the whole lumen of the vessel. The

alveolar walls showed considerable increase of connective tissue about bloodvessels and bronchi. In some regions the alveolar walls were almost avascular. Frothingham notes that the lesions in this case were different from ordinary arteriosclerosis, also from syphilis and from other cases of thrombosis of the pulmonary artery and suggests that it may possibly represent a unique lesion of the pulmonary arteries. He states that it resembles more closely thromboangiitis obliterans than any other condition.

MacCallum[17] has reported a case of "obliterative arteriolosclerosis" of the lung. He says that this obscure condition has been found only once in 12,000 autopsies at the Johns Hopkins Hospital, and that only 40 to 45 similar cases have been reported in detail. The essential clinical and pathologic features of his case are as follows: A colored woman, aged 39 years, complained of great breathlessness and pain about the heart upon exertion. If the exertion was continued, loss of consciousness followed. Physical examination showed moderate dyspnea and cyanosis. The superficial veins of the neck were engorged and pulsating. Fine moist râles were heard at the bases of both lungs behind. The heart was enlarged both to the right and to the left, the pulmonic second sound was accentuated and the closure of these valves easily palpable. The liver was enlarged and there was slight polycythemia. The electrocardiogram showed right ventricular preponderance. At the postmortem examination the heart was found to be much enlarged, the right auricle enormously distended. The right ventricular wall was 8 mm. thick and the left 12 mm. The mitral and aortic valves and coronaries were normal. The pulmonary artery was thickened and much dilated. The liver visibly collapsed when the venæ cavæ were cut. The most important finding was a widespread obliterative arteriolosclerosis.

A somewhat similar case came under our observation. A man, aged 38 years, entered the Colorado General Hospital complaining of shortness of breath, pain in the stomach and asthma of many years' duration. Physical examination showed moderate dyspnea and cyanosis, many râles, asthmatic in type, throughout both lungs, a slightly enlarged heart with faint diastolic and doubtful pre-systolic murmurs, edematous lower extremities. The Wassermann reaction was negative; hemoglobin, 115 per cent; red blood cells, 6,950,000 to 7,250,000. The electrocardiogram indicated right ventricular preponderance. He went steadily downhill and died with signs of failure of the right side of the heart.

At the postmortem examination, the right auricle was greatly dilated, the right ventricle was dilated and hypertrophied, its wall measured 8 mm. in thickness. The pulmonary orifice was slightly dilated. The aorta, the pulmonary artery and its large branches, the pulmonary veins, coronary arteries and heart valves were all

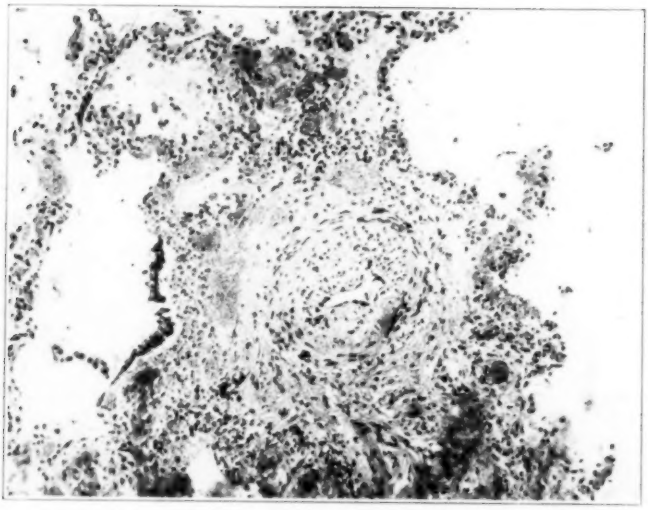

FIG. 2.—Vascular lesion showing thickening of the vessel wall with narrowing of the lumen. (× 50.)

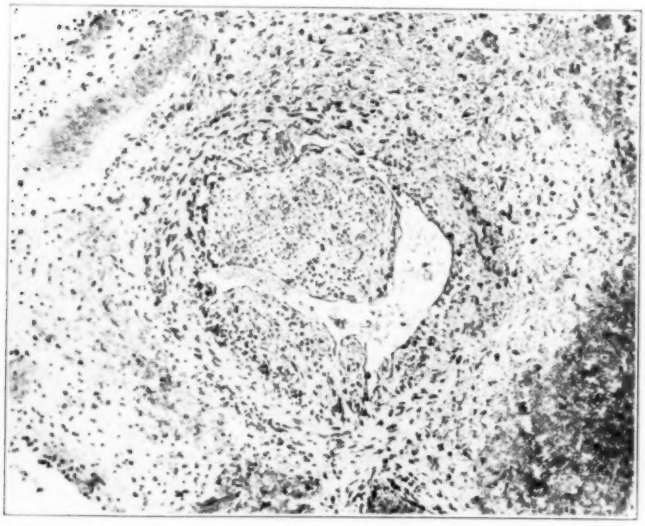

FIG. 3.—Small pulmonary artery showing thickening of the intima and infiltration with leukocytes. (× 100.)

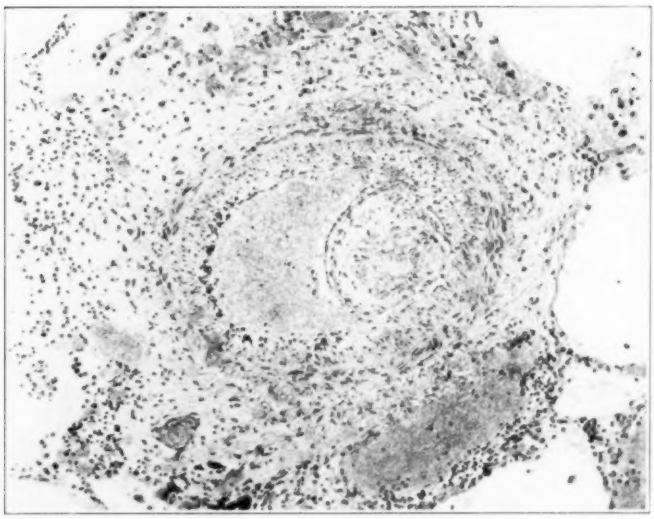

FIG. 4.—Small pulmonary artery showing circumscribed intimal change with partial obstruction. (× 100.)

normal. Almost all of the smaller pulmonary arteries and pulmonary arterioles showed varying degrees of an inflammatory process causing partial or complete occlusion of these vessels. Practically all vessels intermediate in size between the arterioles and arteries, 1 to 2 mm. in size, showed some degree of intimal thickening and many contained hyalin thrombi. Histologically the lesion was not a typical arteriosclerotic process but essentially an inflammatory fibrous intimal thickening with partial or complete occlusion of arteries and arterioles and with thrombosis of larger, otherwise normal, arteries. Neither fat nor lipoid was demonstrated in the lesions (Figs. 2, 3 and 4).

Although the etiology of these differing vascular lesions is obscure, these 3 cases (MacCallum's, Frothingham's and our own) demonstrate that obstruction in the smaller arteries and arterioles eventually produces chronic anoxemia and right ventricular hypertrophy.

IV. Processes Which Affect Primarily the Capillary Bed. Thus far we have considered those forms of obstruction in the lesser circulation in which the location of the obstruction is more or less distant from the capillary bed. In these instances the capillary bed is affected indirectly, since the pulmonary arterial current is blocked higher up. The capillary bed may also be reduced by diffuse lesions which involve it primarily. These lesions, if they are sufficiently extensive and slowly progressive, may likewise by their mechanical obstructive action produce right ventricular hypertrophy and by direct obliterating effect upon the capillaries interfere with oxygenation. The clinical expression of all this will be again the syndrome of cyanosis, dyspnea and right ventricular hypertrophy, with the addition of polycythemia, provided constitutionally depressing influences, such as those which are usually associated with infectious processes, do not interfere with blood formation. Representative of these conditions are extensive pulmonary fibroses and the pathologic processes found in severe long-continued chronic bronchitis, asthma and emphysema. Yegge and one of us (J. J. W.[18]) recently reported a case of this latter type in which the effects of obstruction in the capillary bed were greatly exaggerated by hard work and the low oxygen tension of high altitude. This patient, a lumberjack, long a sufferer from bronchial asthma, who had worked for many years at 10,000 feet altitude, showed the clinical complex of intense cyanosis, dyspnea, polycythemia (maximum red cell count, 8,350,000), somnolence and right ventricular hypertrophy. At the postmortem examination the right ventricular wall measured 14 mm. and the heart valves were normal, the pulmonary artery and all its branches were greatly dilated. The lungs showed marked emphysema, much pulmonary fibrosis, and the typical picture associated with bronchial asthma, namely, thickening and hyalinization of the basement membrane of the bronchi, hypertrophy of the smooth

muscle in the bronchial walls, infiltration of the bronchial walls with lymphocytes and eosinophils. The bone marrow showed moderate hyperplasia. The clinical diagnosis in this case was failure of acclimatization because of hard work at a high altitude, secondary polycythemia, cardiac decompensation, emphysema and bronchial asthma, terminal bronchopneumonia.

Summary. 1. Primarily obstructive lesions of the pulmonary circulation which involve extensively the pulmonary capillaries or pulmonary arteries and are not immediately fatal: (*a*) Raise the pulmonary arterial pressure and produce hypertrophy of the right ventricle, and (*b*) interfere with respiratory function and produce anoxemia.

2. The clinical evidence of chronic anoxemia are commonly dyspnea, cyanosis and polycythemia, rarely precordial pain and syncope.

3. Signs of slowly developing strain upon the right side of the heart in the absence of other obvious cause, such as valvular defects, suggest obstruction in the lesser circulation.

4. Whether the obstruction be in the capillaries, as in certain instances of so-called Ayerza's disease, or in the arterioles and small arteries, as in MacCallum's case, Frothingham's case, and our case here reported, or whether the obstruction be in the larger divisions of the pulmonary arteries, as in the case of Means and Mallory, the underlying clinical picture of chronic anoxemia and failure of the right side of the heart is essentially the same.

5. This survey of the symptoms of obstruction in the lesser circulation has been undertaken to emphasize the too frequently forgotten importance of the integrity of the pulmonary circulation in the process of oxygenation.

BIBLIOGRAPHY.

1. Dunn, J. S.: Quart. J. Med., 1920, **13**, 129; J. Physiol., **53**, 5, 1919.
2. Underhill, S. W. F.: Brit. Med. J., **2**, 779, 1921.
3. Mann, F. C.: J. Exp. Med., **26**, 387, 1917.
4. Binger, C. A. L., Brow, G. R., and Branch, A.: J. Clin. Invest., **1**, 127, 155, 1924–1925.
5. Schlaepfer, K.: Bull. Johns Hopkins Hosp., **33**, 321, 1922; Arch. Surg., **6**, 358, 1923; Surg., Gynec. and Obst., **37**, 510, 1923; Ibid., **42**, 679, 1926.
6. Haggart, G. E., and Walker, A. M.: Arch. Surg., **6**, 764, 1923.
7. Rokitansky, C.: Pathological Anatomy, New Sydenham Society, Swaine's translation, **1**, 316, 1854.
8. Sauerbruch, F., and Bruns, O.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., **23**, 343, 1911.
9. Lundsgaard, C., and Möller, E.: J. Exp. Med., **36**, 559, 1922.
10. Means, J. H., and Mallory, T. B.: Ann. Int. Med., **5**, 417, 1931.
11. Ulrich, H. L.: Ibid., **6**, 632, 1932.
12. Barnes, A. R., and Yater, W. M.: Med. Clin. North America, **12**, 1610, 1929.
13. Jump, H. D., and Baumann, F.: Penna. Med. J., **32**, 754, 1929.
14. Moschcowitz, E.: Am. J. Med. Sci., **174**, 388, 1927; **178**, 244, 1929.
15. Pund, E. R., and Phinizy, T. B.: Ann. Int. Med., **5**, 1391, 1932.
16. Frothingham, C.: Am. J. Path., **5**, 11, 1929.
17. MacCallum, W. G.: Bull. Johns Hopkins Hosp., **49**, 37, 1931.
18. Waring, J. J., and Yegge, W. B.: Ann. Int. Med., **7**, 190, 1933.

COR BIATRIATUM TRILOCULARE WITH RUDIMENTARY RIGHT VENTRICLE, HYPOPLASIA OF TRANSPOSED AORTA, AND PATENT DUCTUS ARTERIOSUS, TERMINATING BY RUPTURE OF DILATED PULMONARY ARTERY.

By Grant O. Favorite, M.D.,
Associate in Pathology, Hahnemann Medical College, Philadelphia, Pa.

(From the Department of Pathology, Hahnemann Medical College and Hospital.)

Cor biatriatum triloculare is a heart with two auricles and one ventricle. A variation of this type of cardiac anomaly is one which has a rudimentary ventricle as well as a common large ventricle. Although anatomically this is a 4-chambered heart, for practical purposes it functions mostly as a 3-chambered organ. One or the other of the great vessels (usually the aorta) arises from the rudimentary ventricle. Because of the rarity of this type of anomaly, and also because of the unusual termination by rupture of the pulmonary artery, the following case is reported.

Case Report. *Past History.* Andrew T., was born in Hungary on September 21, 1913. His father is living and well; his mother died in 1916 of heart disease, age unknown. One older sister, who has supplied most of the information concerning the early history of the patient, is in good health. Two brothers died shortly after birth, cause unknown.

From birth the patient was a typical "blue baby." The cyanosis persisted throughout life, being aggravated by exertion and cold weather. Although he could perform the usual duties incident to childhood, his activities were curtailed by dyspnea and palpitation on moderate exertion. According to his sister, he was a bright boy in school, and always made good marks. He graduated from junior high school at 17. This may seem contradictory, but it may be said that his life was beset with domestic difficulties, which were not conducive to studious application. In the evenings he would sell papers and work in a toy shop. After graduation from school he sought work in various cities. It was during this period that he collapsed in the streets of Philadelphia, and was rushed immediately to the hospital on April 10, 1932. For 1 week prior to his collapse he had a non-productive cough.

Physical Examination. On admission to the hospital the patient was suffering with intense precordial pain and dyspnea. The pulse rate was 110; the respirations, 24; the temperature, 97.3° (axillary). Examination revealed a well-developed, well-nourished youth, apparently in agony. The entire body presented a dusky hue, and the lips and extremities were distinctly cyanotic. The fingers and toes showed pronounced clubbing. The pupils reacted normally. The buccal mucous membrane was deeply injected. The lungs showed impaired resonance and râles at the bases posteriorly. The area of cardiac dullness was increased to the right and left. The great vessel area also appeared to be increased. Auscultation revealed a systolic murmur in the pulmonic area, accompanied by a thrust. A diastolic murmur was heard in the aortic area. The systolic blood pressure was 80 mm., the diastolic, 60. The pulse was regular in rate, force, and rhythm.

Laboratory Findings. An electrocardiogram (Fig. 1) taken on the following morning was interpreted by Dr. G. D. Geckeler as follows: "Normal sinus rhythm with *Q-R-S* complexes in Leads II and III of exaggerated amplitude (often seen in cases of congenital heart disease and aortic insufficiency). All waves are deformed by induction house current. How much effect this has in changing the character of the *P* waves in Leads II and III, and of the *T* waves in the same leads, is questionable. *P-R* interval measures 0.18 second, and the *Q-R-S* interval measures 0.9 second. Unfortunately, the patient died before another tracing could be made."

A roentgenogram of the chest (Fig. 2) showed an enormous enlargement of the heart and great vessels. The peculiar outline of the cardiac shadow is accounted for by the unusual shape of the heart and the hemopericardium found at autopsy.

The hemoglobin was 100 per cent (standard = 16.92 gm. hemoglobin per 100 cc.). Unfortunately, a red blood count was not made. The white blood cells numbered 12,900; the polymorphonuclears, 71 per cent; lymphocytes, 27 per cent; transitionals, 2 per cent. The blood Wassermann and Kahn tests were negative. The chemical examination of the blood revealed the following findings: glucose, 125 mg.; urea nitrogen, 23 mg.; creatinin, 2 mg., per 100 cc. of blood. The urine showed a faint trace of albumin, pus cells, and several hyalin and granular casts.

Course. The patient lived for 28 hours from the time of admission. The pain and dyspnea continued unabated. The cyanosis increased. Vomiting occurred on several occasions. The axillary temperature varied from 99° to 100°. The pulse reached its highest rate of 120 a few hours before death. The respirations fluctuated between 24 and 40. One-half hour before death the patient was still complaining of severe precordial pain. At the time of his death his age was 18 years, 6 months and 20 days.

Autopsy Findings. (Autopsy performed approximately 20 hours after death.) The body is that of a fairly well-nourished, well-developed, young male adult, about 20 years of age. There is cyanosis of the lips and fingers. The fingers and toes present drum-stick enlargement of their distal third. This clubbing is rather extreme, and the fingers are affected to a greater degree than the toes. The panniculus adiposus is well preserved.

Exploration of the thoracic cavity reveals the following:

Heart. The cardiac area is enlarged in all directions, but lies chiefly on the left side. The pericardium is distended and has a reddish-blue color. On opening the pericardium, its cavity is filled with approximately 800 cc. of bloody fluid and blood clots. Around the base of the great vessels, the clots are quite adherent to the underlying structures. Careful removal of these clots reveals a markedly dilated, and ruptured pulmonary artery as the source of hemorrhage. The visceral pericardium covering this vessel has two longitudinal tears on the anterior surface, and another similar tear on its posterior surface. It is separated from the structures beneath by clotted blood. The wall of the pulmonary artery contains multiple ruptures, which will be described in more detail later. Other features noted at this time are aortic hypoplasia and patent ductus arteriosus. The heart is hypertrophied and has a globular shape, with a blunted apex. No ventricular division can be discerned by external examination (Figs. 3, 4).

A closer study of the specimen several days later, after preservation in Kaiserling solution, reveals the following additional findings: The heart, including part of the descending aorta and main pulmonary branches as shown by the photographs and diagram, weighs 700 gm. When immersed in water it displaces 950 cc. of fluid.

Auricles. Both auricles are hypertrophied. The right auricle presents no anomalies, while the left has two pulmonary veins emptying into the cavity instead of the usual four. The interauricular septum has an anatomi-

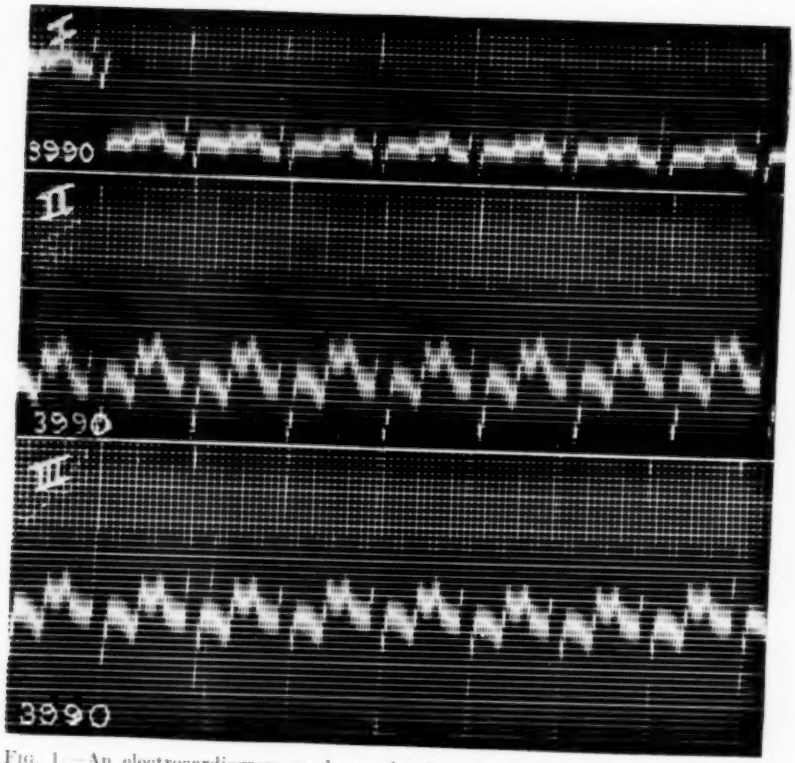

FIG. 1.—An electrocardiogram made on the day of the patient's death, showing exaggerated amplitude of the *Q-R-S* complex in Leads II and III.

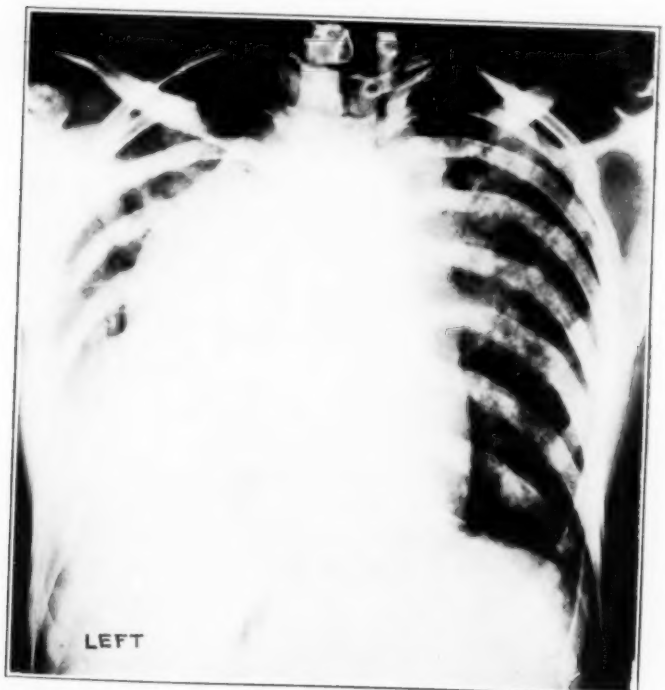

FIG. 2.—A roentgenogram of the patient made on the day of his death. Note the enormous enlargement of the cardiac and great vessels shadow.

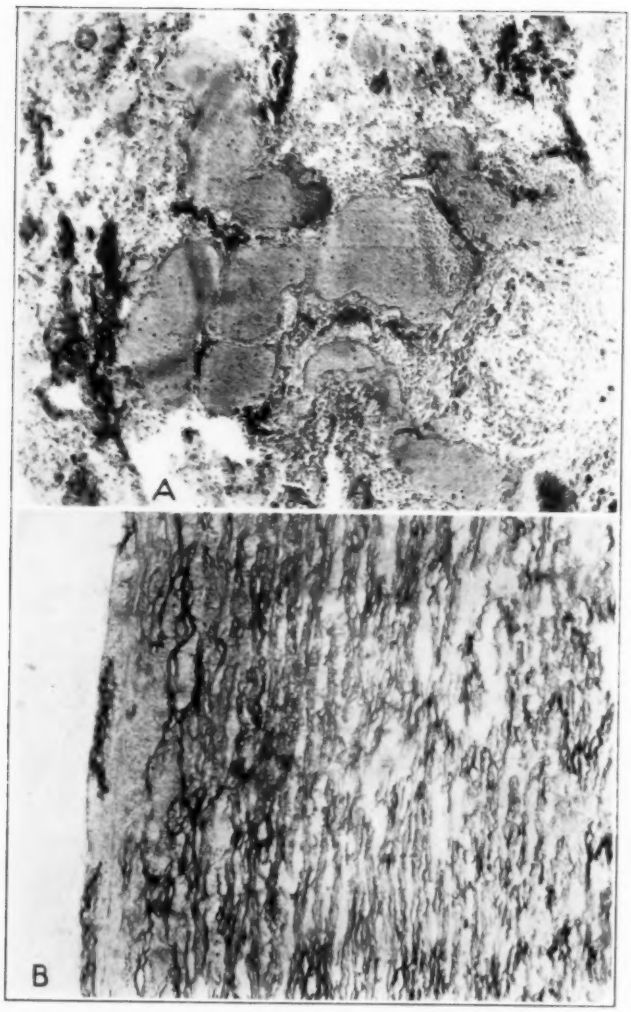

FIG. 6.—*A*, A photomicrograph showing the marked dilatation of the smaller vessels of the pulmonary circulation. *B*, A photomicrograph of a section of the pulmonary artery stained with Weigert's stain, showing fragmentation of the elastic fibers.

cally patent foramen ovale with overlapping edges. On the left side of the septum, one of the edges is supported by a short band which appears to be a continuation of the valve. Functionally, it is doubtful that admixture of auricular blood existed during life.

Ventricles. For all practical purposes one large ventricle exists, and contains the tricuspid, mitral and pulmonary orifices. On the extreme upper right quadrant is found a small ventricle containing the aortic orifice.

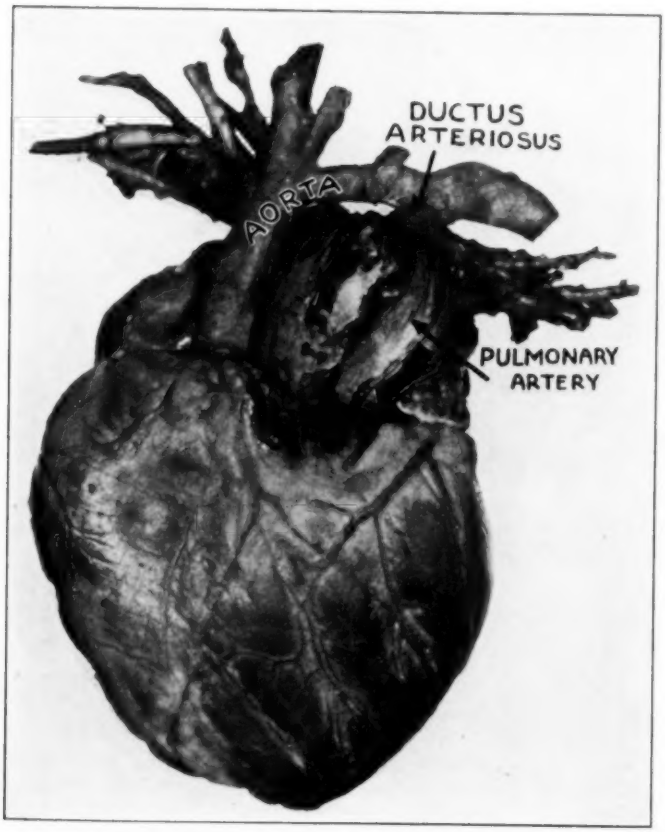

FIG. 3.—A photograph of the specimen, showing the globular shape of the heart, the dilated and ruptured pulmonary artery, transposition and hypoplasia of the aorta, and the patent ductus arteriosus.

The ventricles communicate by an interventricular septal defect at the base. The large ventricle has inside measurements of approximately 9 by 4 by 10 cm. The ventricular wall measures 2.1 cm. with trabeculæ, and gradually tapers to 0.6 cm. at the apex. The small ventricle measures approximately 3 by 3 by 6 cm. Its wall measures 1.2 cm. at the middle, and 0.4 cm. at the apex.

Septum. The interventricular septum is well developed below. Its upper third is absent and is replaced by an opening approximately 2 cm.

in diameter. A fenestrated appearance is imparted to this septal defect by the traversation of chordæ tendineæ of the tricuspid valve.

Valves and Orifices. The tricuspid orifice connects the right auricle with the large ventricle and is adjacent to the septal defect. The tricuspid ring measures approximately 4 cm. in diameter. The valve has a right and left leaflet of about equal size, and a smaller one posteriorly. The chordæ tendineæ of the right leaflet are partly attached to the interventricular septum, below the edge of the defect. When the valve is open, the right leaflet with its chordæ tendineæ partly closes the defect. The mitral ring measures approximately 3 cm. in diameter. The valve consists of a right and left leaflet. The chordæ tendineæ of the right leaflet are attached to

FIG. 4.—A photograph of the base of the heart viewed from below, showing the common ventricle, the defective septum, rudimentary ventricle, and the various orifices.

columnæ carneæ on the anterior and posterior ventricular walls. The pulmonary orifice arises from the large ventricle, between the tricuspid and mitral orifices, and anteriorly to them. Its diameter measures 2.5 cm. at the base of the semilunar valves. The valves show no anomalies.

Pulmonary Artery. The pulmonary artery shows a marked dilatation and multiple ruptures. The outside diameter slightly above the base measures 4.3 cm., while at the point of greatest enlargement, above the ruptures, it measures 5.6 cm. laterally, and 3.6 cm. anteroposteriorly. The ruptured portion of the artery is enveloped in blood clots. The visceral pericardial layer is separated from the structures beneath, and presents two irregular vertical tears anteriorly, and one posteriorly. The artery has a shattered appearance with complete separation of the wall. On the

anterior surface, 2.3 cm. from the base, there is a transverse linear tear involving about one-half of the anterior circumference. Another linear tear extends downward to the level of the semilunar valves. On the posterior surface, a diagonal irregular tear starts at the level of the transverse tear, and runs upward and to the right, to the level of the bifurcation of this vessel.

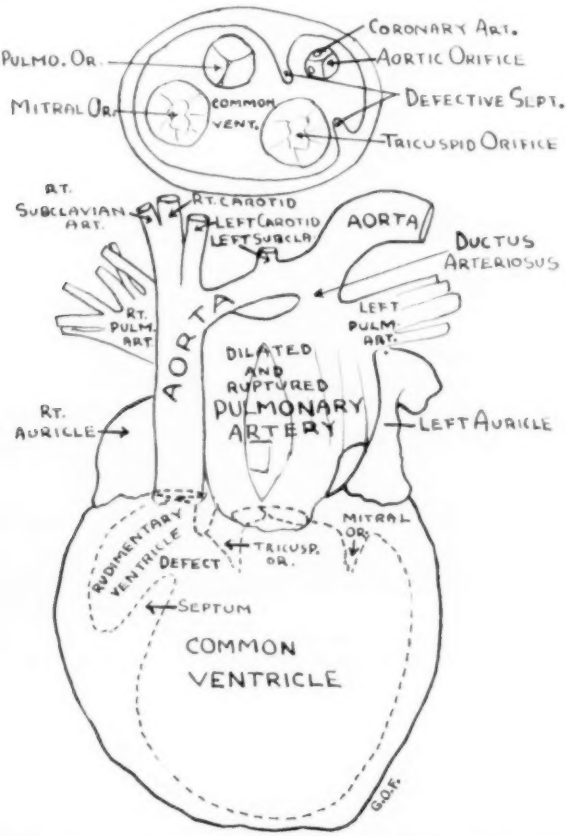

FIG. 5.—The upper diagram is a schematic representation of the base of the heart viewed from above. It shows the relative position of the various orifices. The aorta is transposed to the right into the rudimentary ventricle, and lies in the same plane as the pulmonary artery. The tricuspid, mitral, and pulmonary orifices are located in the common left ventricle. The lower diagram shows the other features of the heart and vessels.

The branches of the pulmonary artery appear short and dilated. The left branch measures 1.5 cm. in length and 2.5 cm. in diameter. It breaks up abruptly into numerous small radicles. The right branch is 2.5 cm. long and 2.5 cm. in diameter. It gives off 4 small branches. After continuing for a distance of 1.2 cm. it also breaks up abruptly into numerous small radicles.

Aorta. The aortic orifice is located at the base of the small ventricle, 1.2 cm. from the septal defect. It measures 0.9 cm. inside diameter, at the

base of the semilunar valves. The aorta is hypoplastic and is transposed to the right. The vessel gradually diminishes in size and reaches its smallest outside diameter at the arch, between the left common carotid artery and the left subclavian artery. Here it measures 0.7 cm. in diameter. Incidently, these vessels are widely separated, the left common carotid arising near the base of the innominate artery. Beyond the ductus arteriosus, the aorta measures 1.8 cm. in external diameter. The aortic semilunar valves are 3 in number, 1 anteriorly, and 2 laterally. The coronary arteries arise behind the anterior and the left semilunar cusps.

Ductus Arteriosus. The ductus arteriosus is well developed and has a rather wide lumen. It measures 0.3 cm. in length and 0.8 cm. in diameter.

The remainder of the autopsy findings are relatively unimportant. The lungs are dark red in color and congested. On section, a frothy, serosanguinous fluid exudes. The gastro-intestinal tract is negative. The liver is slightly larger than normal. On section, it presents a congested appearance. The gall bladder, pancreas, adrenals, and spleen are grossly normal. The kidneys are normal in size and shape. The capsule strips off easily, revealing a dark red, smooth surface. On section, there is general congestion. The urinary bladder, prostate, and ureters are grossly normal.

Microscopic Examination. The lungs reveal a generalized edema. The smaller vessels are markedly dilated and distended with blood. The sections of the pulmonary artery taken near one of the ruptures show hemorrhagic infiltration of the adventitia and the adjacent media. The media is edematous and its fibers are widely separated. Sections stained with Weigert's stain show fragmentation and separation of the elastic fibers. The liver shows passive congestion limited to the central zone of the lobules. The kidneys have congested capillaries and cloudy swelling of the tubular epithelium (Fig. 6).

Summary of Salient Features. The auricles, through their respective auriculoventricular orifices, communicate with a large common ventricle. The foramen ovale is anatomically patent, but is probably closed functionally. The pulmonary artery is dilated, ruptured, and arises from the common ventricle. A septum, defective at the base, separates this ventricle from a rudimentary one situated in the upper right quadrant. A transposed and hypoplastic aorta arises from the base of the rudimentary ventricle. The ductus arteriosus is widely patent, while the pulmonary veins are two in number. The smaller vessels of the pulmonary circulation are dilated.

Review of the Literature. Since cardiac anomalies are numerous and concomitant, it is possible that this condition may have been described under other titles. Abbott[1] was able to collect 11 similar cases. A careful search of the literature failed to add to this number. The author has been able to study the original reports of 10 of the 11 cases. Not all of these cases were identical in their main anomalies. For the sake of comparison, we have used the following anatomic criteria: (1) a common large ventricle, receiving the auriculoventricular orifices and the orifice of one of the great vessels; (2) defective interventricular septum; (3) one of the great vessels leading into the rudimentary ventricle.

Seven cases conformed with the above requirements. Holmes'[2] patient was a male, aged 22. This case is unique, because the pulmonary artery springs from the rudimentary ventricle. Peacock's[3] patient was a child aged 8 months, while Rokitansky's[4] was a male aged 30 years. In addition, Rokitansky's case presented anomalies

of the openings of the vena cava and the pulmonary veins. Marchand's[5] and one of Spitzer's[7] cases were practically identical with ours. Another case described by Spitzer[6] was that of a child aged 5 months, and lacked a tricuspid opening. Mill's[8] patient was a child, who, in addition to the major defects, also had 3 coronary arteries and coarctation of the aorta.

The other 4 cases included in this group by Abbott[1] are those of Rokitansky (second case), Chiari, Theremin, and Mann. Chiari's report was not available to the author. A study of the other 3 cases shows that they resemble more closely the true cor biatriatum triloculare, since all ventricular orifices originate in the same ventricle. Theremin's[9] patient was an infant aged about 2 months. Rokitansky[10] described the heart of a girl aged 10 years, in which the narrow aorta, a stenotic pulmonary artery, and the atrioventricular orifices communicated with a large right ventricle. The case reported by Mann,[11] and also by Young[12] was that of a male aged 35 years. The heart weighed $1\frac{3}{4}$ pounds, and had a small fossa in the right upper quadrant continuous with the large common ventricle. Mann[11] cites similar cases by Kreyzig[13] and Duroziez.[14]

From the standpoint of rupture of the pulmonary artery the literature is quite meager. A careful survey revealed 8 cases. Dowse[15] described the case of a young woman without history of syphilis. The pulmonary artery presented an aneurysmal sac, about the size of a hen's egg, with a rent in the outer wall. The pulmonary valves were covered with vegetations. Duffield,[16] in reviewing the literature of dilatation of the pulmonary artery found 4 cases of rupture, including that of Dowse's. The other 3 cases with Duffield's references follow: Ambroise Paré (Observations on Aneurisms, by John E. Ericksen, London, 1844) described the case of a tailor, who, while playing ball died from rupture of the pulmonary artery. Adam's reference (second volume of *Trans. Calcutta Med. Soc.*) contained no comment, while Dlauhy's patient (*Viertlj. f. Prakt. Heilk.*, 1848) presented an aneurysm with rupture. No mention of congenital cardiac defects was made.

Arró[17] reported a case in 1882, entitled, "Rotura de la Arteria Pulmonar, Muerta Fulminante." The reference was obtained from the Index Medicus; original publication was not available, but the title is self-explanatory. Durno and Brown[18] described the case of a man, aged 33, who had a dilated and atheromatous pulmonary artery, with a small hole near its base. The pericardial cavity was filled with blood. Moench's[19] case was a woman aged 29 years with hemopericardium, widely patent ductus arteriosus, and aneurysmal dilatation and rupture of the artery. Vogt-Møller's[20] case report concerns a girl, aged 4 years with sepsis (streptococcic), congenital cardiac hypertrophy, localized minimal abscesses of the pulmonary artery and aorta followed by perforation of both vessels, and resulting in hemopericardium, heart tamponade, and death.

Comment. For the consideration of the pathogenesis of congenital heart disease the reader is referred to standard works on the subject, notably the monographs by Abbott[1, 21] and Spitzer.[22, 23] Of great importance are Spitzer's contributions, whose theory, as reviewed by Abbott,[1] is based on the phylogenetic relationship existing between the human and reptilian heart. A portion of the right ventricle representing the conus of the reptilian right aorta is closed in the normal human embryo by the clockwise torsion of the bulboventricular end of the primitive cardiac tube. Failure of the normal degree of torsion or "detorsion" results in the apparent shunting of the parts in counterclockwise direction, which not only brings the parts out of their normal position, but reopens the channel of the reptilian right aorta and obliterates the left ventricular aortic trunk normally present in the human heart. In lesser degrees of detorsion both trunks persist, fuse, and form an abnormally large aorta riding over the septum. Spitzer supports his contention with a graded series of 11 cases, dividing the various grades into 5 types. Two of his cases, which are similar to ours, he groups under Type IV, a "mixed" transposition whereby the pulmonary artery and the tricuspid valve are found in the mitral valve ventricle.

An analysis of the 7 cases that were similar to ours reveals the following points of interest. The age varied from 5 months to 30 years. The sex was mentioned twice, both being males. The status of the foramen ovale was cited in 5 cases, and it was found to be opened in 2 (Holmes,[2] Spitzer[6]); the ductus arteriosus was mentioned in 5 cases, and found patent in 3 (Spitzer,[6,7] Mills[8]). Other associated defects were anomalous openings of the vena cava and pulmonary veins (Rokitansky[4]), absence of the tricuspid orifice (Spitzer[6]), coarctation of the aorta, and supernumerary coronary arteries (Mills[8]).

Spontaneous rupture of the pulmonary artery from any cause is extremely rare. Moench,[19] in 1924, found 2 additional cases besides his own (reference of 1 was not given). The author was able to collect 8 cases from the literature. The available records failed to show the association of major cardiac anomalies with rupture of the pulmonary artery. In Moench's case, and in ours, the ductus arteriosus was widely patent. The rupture in the other cases was associated with small abscess of the arterial wall, aneurysmal dilatation of obscure etiology, and atheromatous changes.

Dilatations and aneurysms of the pulmonary artery are rather common. Henschen,[24] in 1906, collected 42 cases. Among recent reports may be mentioned those of Corsy,[25] Coleschi,[26] and Crouzon and Grenaudier.[27] Moench[19] believes that a patent ductus arteriosus is a most important factor in the etiology of dilatation, and incidently, rupture, since many cases present such a defect. Certainly, this must have been true in our case. No doubt, the major portion

of the systemic blood flowed through the pulmonary artery and the ductus arteriosus, as the ascending and transverse aorta was hypoplastic. The added strain placed on the pulmonary artery eventually caused its dilatation and rupture. Other explanations, however, must be sought in those cases where there is a persistent patent ductus arteriosus without other congenital defects.

Summary. A young man, aged 18 years, was taken ill suddenly, suffering with an agonizing pain of 28 hours' duration, and presenting symptoms of congenital heart disease. The autopsy revealed hemopericardium and a large heart, with dilatation and rupture of the pulmonary artery, hypoplasia and transposition of the aorta, and a widely patent ductus arteriosus. The heart presented a variant of cor biatriatum triloculare, having a rudimentary right ventricle which gave origin to the aorta. The literature is reviewed from the standpoint of the cardiac anomaly and rupture of the pulmonary artery.

I wish to express my appreciation to Dr. M. E. Abbott for the helpful suggestions in the preparation of the article, and to Dr. L. W. Falkinburg for the translation of the German literature.

REFERENCES.

1. Abbott, M. E.: Nelson's Loose-leaf Living Medicine, Vol. 4, New York, Thomas Nelson & Sons, 1928.
2. Holmes, A. F.: Montreal Med. J., **30**, 522, 1901. Reprinted by Abbott from Trans. Medico-Chir. Soc. of Edinburgh, 1824.
3. Peacock, T. B.: Trans. Path. Soc., London, **6**, 117, 1854–1855.
4. Rokitansky, C. F.: Defekte der Scheidewände des Herzens, Vienna, p. 29, 1875.
5. Marchand, F.: Deutsch. path. Gesellsch., **12**, 174, 1908.
6. Spitzer, A.: Virchow's Archiv f. path. Anat. **243**, 236, 1923.
7. Spitzer, A.: Ibid., p. 243.
8. Mills, E. S.: J. Med. Res., **44**, 257, 1923.
9. Theremin, E.: Études sur les affections congénitales du coeur, Paris, Observation, 43, p. 76, 1895.
10. Rokitansky, C. F.: Defekte der Scheidewände des Herzens, Vienna, p. 27, 1875.
11. Mann, J. D.: Brit. Med. J., **1**, 614, 1907.
12. Young, A. H.: J. Anat. and Physiol., **41**, 190, 1907.
13. Kreyzig: Krankheiten des Herzens, Vol. 3, 1817. Quoted by Mann.
14. Duroziez: J. de Conn. méd. prat., Paris, 1885. Quoted by Mann.
15. Dowse: Lancet, **2**, 660, 1874.
16. Duffield, J. E.: Am. J. Med. Sci., **83**, 77, 1882.
17. Arró: Rev. de cien. med., Barcelona, **8**, 703, 1882.
18. Durno, L., and Brown, W. L.: Lancet, **1**, 1693, 1908.
19. Moench, G. L.: J. Am. Med. Assn., **82**, 1672, 1924.
20. Vogt-Møller, P.: Hospitalstidende, **73**, 371, 1930.
21. Abbott, M. E.: Osler's Modern Medicine—McCrae, Vol. 4, Philadelphia, Lea & Febiger, 1927.
22. Spitzer, A.: Virchow's Archiv f. path. Anat., **243**, 81, 1923.
23. Spitzer, A.: Ztschr. f. Anat. u. Entwickl., **84**, 30, 1927.
24. Henschen, S. E.: Aneurysm of the Pulmonary Artery, Samml. klin. Vortr. (Volkman), New Series, 422–423; Inn. Med., 126–127. Quoted by Moench.
25. Corsy, F.: Marseille méd., **48**, 350, 1911.
26. Coleschi, L.: Riforma med., Napoli, **34**, 706, 1918.
27. Crouzon, O., and Grenaudier: Bull. et mém. Soc. méd. d. hôp. de Paris, **46**, 34, 1922.

ENDOCARDITIS DUE TO A NEISSERIA PHARYNGIS ORGANISM.

By Jacob D. Goldstein, M.D.,
INSTRUCTOR IN MEDICINE, SCHOOL OF MEDICINE AND DENTISTRY, UNIVERSITY OF ROCHESTER, ROCHESTER, NEW YORK.

(From the Departments of Bacteriology and Medicine, School of Medicine and Dentistry, University of Rochester.)

Endocarditis due to Gram-negative diplococci other than the gonococcus and the meningococcus is rare. In 1918 Schultz[1] first recorded an instance of acute vegetative endocarditis due to Neisseria pharyngis sicca. In 1932 Graef, de la Chapelle and Vance[2] described a similar case. This report presents the clinical, pathologic and bacteriologic findings in another case of fatal endocarditis due to a similar organism.

Case Report. Patient, J. R. (Unit No. 49813), Italian female, aged 21.

Past History. The patient was first seen in July, 1931. On this occasion the history and findings led to a diagnosis of chronic pelvic inflammatory disease. It was also noted that during the past 1 or 2 years she had experienced dyspnea and palpitation on exertion. Her heart was found slightly enlarged to the left, the precordial thrust was prominent, but no murmurs or thrills were present. The patient was referred to the Gynecological Clinic for treatment, but did not return to the hospital until August, 1932, when she registered in the Obstetrical Clinic. At this time she was 4 months pregnant. In the interim her health had been fairly good.

Present Illness. On August 12, 1932, the patient was admitted to the Rochester Municipal Hospital. She complained of headache, and of pain in the abdomen, back, right shoulder and several finger joints. Her illness had begun suddenly 4 days previously with severe occipital headache. The initial headache was followed within 24 hr. by fever, repeated shaking chills, and generalized muscle and joint pains. The pain became especially severe throughout the back. The abdominal pain, which appeared soon after the first chill, was diffuse, quite constant, and cramp-like in nature. Since the onset, marked urinary frequency and urgency with suprapubic pain and burning had been present.

Physical Examination. The patient was obviously acutely and critically ill. The mouth temperature was 38.2° C. (100.4°F.), the pulse rate 112, the respiratory rate 24. Almost all of the joints were tender on pressure and painful on even slight movement, yet none showed any increased heat, redness or obvious swelling. Examination of the lungs revealed only scattered râles at both bases. The heart was enlarged, the rhythm regular. The blood pressure was 95 systolic, 40 diastolic. Classic signs of stenosis of the mitral valve were present. The abdomen was everywhere tender on pressure, and in the lower quadrants, especially on the right side, some rigidity was noted. The uterus extended 3 finger breadths above the symphysis. Rectal examination revealed moderate diffuse tenderness. The neurologic examination was negative; specifically the neck was not stiff.

The white blood cell count on admission was 26,000 per cmm. with 96% polymorphonuclear neutrophils. The urine contained no sugar or albumin. Numerous epithelial cells, scattered leukocytes, and occasional hyalin and granular casts were noted in the centrifuged specimen.

Course in Hospital. Immediately after admission, the patient was given salicylates both by mouth and intravenously but without any amelioration

of her joint pains. The abdominal pain was most intractable and suggested the possible presence of an acute surgical condition. Operative intervention, however, was judged to be inadvisable. Forty-eight hours after admission the blood culture was reported to be positive, a Gram-negative diplococcus having been recovered in pure culture.

On the 4th day after admission, the joint pains subsided considerably, but the intense abdominal pain persisted and the abdominal distention progressed despite vigorous treatment. On the 5th day drowsiness was first apparent and the next day stiffness of the neck was noted. Lumbar puncture was performed immediately. The spinal fluid, under a pressure of 300 mm. of water, had a ground-glass appearance and contained 450 cells per cmm. Of these 98% were polymorphonuclear leukocytes. A few intracellular and extracellular Gram-negative diplococci were found in the

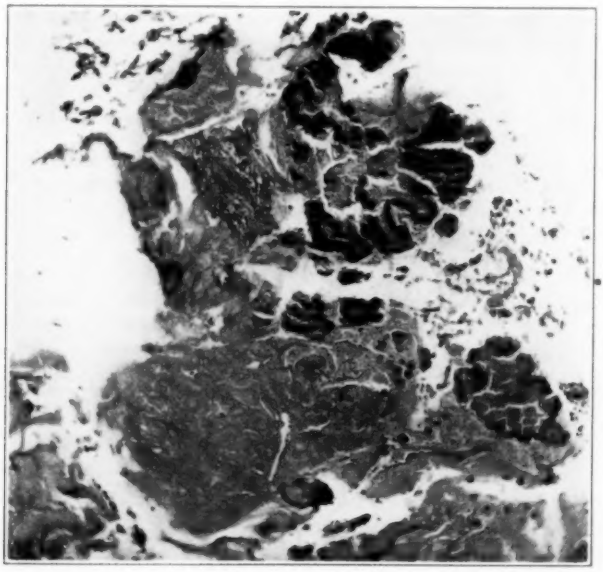

FIG. 1.—Vegetations from mitral valve. Bacterial strain (method of Brown and Brenn). × 100.

stained smears. Despite the fact that the preliminary sugar fermentations with the organism recovered from the blood stream indicated that this diplococcus was not a meningococcus, it was decided to administer antimeningococcus serum. Within a period of 24 hr. the patient received 60 cc. of New York State Antimeningococcus Serum intravenously, and 80 cc. intrathecally. She continued to be intermittently drowsy and delirious, and died on August 22, 1932, 10 days after admission.

Autopsy. The autopsy was performed by Dr. William Allen, August 22, 1932, 3½ hr. after death. The body was that of a young, well-nourished woman. Several small petechiæ were noted on the chest. The peritoneal cavity contained approximately 1000 cc. of clear, amber-colored fluid. Each pleural cavity contained about 1000 cc. of a similar fluid.

Heart. The heart weighed 300 gm. The muscle was grossly normal but microscopically showed numerous minute focal abscesses. The tricuspid,

pulmonic and aortic valves were normal. The mitral valve was moderately but distinctly thickened and deformed. On the margins of the valve and extending down over the chordæ tendineæ were numerous, various sized, grayish, cauliflower vegetations (Fig. 1). Microscopically these areas showed hyalinization of the valve leaflets and vegetations containing large clumps of bacteria. The coronary arteries were normal.

Lungs. The lungs were edematous, but otherwise nothing pertinent was found. *Spleen:* The spleen weighed 350 gm. and contained two small infarcts. In the sections numerous emboli with clumps of polymorphonuclear leukocytes and bacteria were seen in the walls and lumina of the veins. *Liver:* The liver weighed 2300 gm. The cut surface showed many minute yellowish-gray flecks which microscopically consisted of collections of polymorphonuclear leukocytes in areas where hyalin degeneration of the liver cells had occurred. *Pancreas:* The pancreas showed some increase in connective tissue and a few collections of polymorphonuclear leukocytes. *Kidneys:* The kidneys each weighed 200 gm. Several anemic infarcts surrounded by zones of hemorrhage and cellular infiltration were present in the cortex. Many glomeruli showed distinct inflammatory changes. There were also scattered areas of acute focal interstitial nephritis. *Gastro-intestinal tract:* The alimentary tract was normal except for a small infarction in the small bowel. *Brain and spinal cord:* The brain weighed 1300 gm. The smaller vessels on the cerebral and cerebellar surfaces were considerably injected. There were numerous small collections of leukocytes throughout the parenchyma and in the meninges. The spinal cord showed similar collections of cells. *Genital organs:* The uterus contained an unmacerated fetus. Sections of fetal heart, liver and lung showed no evidence of a septicemia.

Anatomical Diagnosis. Subacute vegetative mitral endocarditis. Chronic mitral endocarditis. Infected infarcts of spleen and kidneys. Hyalin emboli in heart and lungs. Early acute meningitis. Glomerulitis, and acute focal interstitial nephritis. Focal necrosis of liver. Early fibrinous pleuritis and pericarditis.

Bacteriologic Studies. Cultures were taken at autopsy from the heart's blood; from the pleural, pericardial, peritoneal, spinal and amniotic fluids; and from practically all of the organs. Gram-negative diplococci were recovered from the heart's blood, from a mitral vegetation, and from a splenic infarct. Direct smears from the mitral vegetations showed large aggregates of Gram-negative diplococci. These organisms were of uniform size, biscuit-shaped, and arranged singly or in pairs. With Gram's stain, they were uniformly and constantly decolorized. After prolonged cultivation a considerable variation in the size of individual organisms occurred, but the staining characteristics remained constant.

Cultural Characteristics. Growth in Douglas' tryptic digest broth during the first 24 hr. was characterized by a faint diffuse clouding. Within the next 24 hr. large granular aggregates had formed at the sides of the tube and had settled to the bottom as a heavy sediment. "String" formation developed as incubation was continued.

Colony Type. On ascitic fluid agar, after 24 hr., the colonies were quite small (0.2 to 0.4 mm. in diameter), convex and finely granular, with a finely scalloped edge. After 48 hr. colony size varied from 0.5 to 1 mm. and a small central depression appeared at the apex

of the convexity. After 72 hr. colonies up to 1.5 mm. in diameter developed. On hemoglobin serum agar and on Bradford's medium (Douglas' agar, ascitic fluid, 20% glucose and defibrinated blood) the colonies were definitely larger and quite moist. On plain blood agar the colonies were always smaller, more opaque, and distinctly less friable.

After 5 weeks' cultivation on the above media with transfers made every 4 days, growth was usually profuse in from 18 to 24 hr. and the colonies on blood agar became as large and moist as those on Bradford's medium. After being cultivated in Douglas' broth for several transfers and then replated, the organism again grew in small, rather dry colonies which in turn again became large and moist after several transfers on enriched solid media.

Fermentation Reactions. For the study of fermentation reactions, ascitic fluid agar slants containing the respective carbohydrates and Andrade's indicator were used. Acid formation was observed in four sugars within 24 hr. (sucrose, glucose, levulose, maltose) and in dextrin within 36 hr. No reaction was noted in any of the other carbohydrates tested (mannite, dulcite, galactose, inulin, lactose).

Virulence for Laboratory Animals. Graded doses of freshly grown organisms were injected intraperitoneally into mice without producing any ill effects. The largest dose given to each of 2 mice was the washings from one ascitic fluid agar slant after 24 hr. of incubation. The washings from two similar agar slants were given without effect to each of 3 guinea pigs. One rabbit, used for the production of an immune serum, did not have any unfavorable reaction to any of the injections.

Serologic Reactions. *Agglutination.* Agglutination reactions with this organism were not carried out since spontaneous clumping occurred in normal salt solution.

Precipitation. Immune serum was prepared by giving a large male rabbit over a 40-day period a series of 10 intravenous injections of whole organisms washed from 24-hr. ascitic fluid agar slants. The antigen for use in precipitation tests was prepared as follows: The 24-hr. growth on an ascitic fluid agar slant was washed with saline and inoculated into each of two flasks containing 100 cc. of Douglas' broth. After growth for 48 hr. the broth from one flask was centrifuged free of organisms and the cells added to the second flask. One-half cubic centimeter of pure phenol (0.5%) was added and the incubation resumed for 5 days. The broth was then centrifuged and the clear supernatant fluid used as the antigen in the precipitation reactions. This material in a dilution of 1 to 256 gave a clear-cut precipitin reaction with the homologous immune serum.

In addition to the strain of Neisseria pharyngis obtained from the patient described in this report, two other strains were available for comparison. One of these, sent from Dr. F. B. Mallory's laboratory in Boston by Dr. M. S. Shiling, also came from a fatal case of

endocarditis. The other strain was supplied by Dr. G. W. Rake of the Rockefeller Institute, and was isolated from the throat of a normal individual. Dr. Rake considered this organism characteristic of Neisseria pharyngis sicca, insofar as the descriptions of this organism in the literature permit the use of the term "characteristic." For the purpose of control, antigens were similarly prepared from typical stock strains of Neisseria catarrhalis and Neisseria meningitidis. Thus in the precipitation reactions, 5 antigens all prepared according to the technique described above, were used as follows:

1. Antigen J. R., organism recovered from patient, J. R., the subject of this report.
2. Antigen Shiling, furnished by Dr. M. S. Shiling.
3. Antigen Rake, furnished by Dr. G. W. Rake.
4. Antigen catarrhalis, stock culture of N. catarrhalis.
5. Antigen meningitidis, stock culture of N. meningitidis (a mixture of 3 strains).

Using these 5 antigens precipitation tests, carried out with 6 sera, yielded the following results:

1. *Serum from patient J. R.* This serum contained no precipitin for any of the antigens prepared.

2. *Serum from rabbit immunized with organism J. R.* A positive precipitation to a titer of 1 to 256 was obtained with the homologous antigen. No crossing with the other antigens was observed.

3. *Serum from Dr. Shiling's patient.* A positive precipitation to a titer of 1 to 256 was obtained with the homologous antigen. Crossing occurred at a titer of 1 to 16 with antigens J. R. and Rake, but not with the other antigens.

4. *Serum from rabbit immunized with Dr. Shiling's organism.* A positive precipitation to a titer of 1 to 64 was obtained with the homologous antigen. Crossing occurred at a titer of 1 to 16 with antigen catarrhalis and at a titer of 1 to 4 with antigens J. R. and Rake.

5. *Commercial antigonococcus serum* and (6.) *New York State antimeningococcus serum:* These sera contained no demonstrable precipitins for the antigens used.

Discussion. Considerable variations after only a moderate number of transfers on artificial media are known to occur among Gram-negative organisms found in the nasopharynx.[3] The organism from the patient, J. R., showed these variations in colony characteristics, growth rate, and in the size of the individual organisms. At some stage in this varied state, a close similarity to various "typical descriptions" of Neisseria pharyngis sicca and to other unclassified[4] nasopharyngeal Gram-negative diplococci was found.

The patient did not develop in the blood any demonstrable precipitin against the infecting organism. The immune rabbit serum prepared with the J. R. organism contained precipitin only for the

homologous antigen, and no cross-reactions with the other antigens were found. The serum of Dr. Shiling's patient, however, developed a titer of 1 to 256 with the homologous antigen and showed some crossing with both the J. R. and Rake antigens.

The organisms received from Drs. Shiling and Rake were studied as to growth characteristics and sugar fermentations, in addition to the precipitin reactions. The sugar reactions were similar and constant on subculture for all three organisms. Colony type and size on different media varied no more than the cycle of changes noted on repeatedly subculturing on various media the J. R. organism alone. At some stage in the various manipulations, especially after several transplants on enriched solid media, all three organisms looked quite similar.

While these minor variations in cultural characteristics and perhaps in the precipitin reactions may depend solely upon environmental factors, it is suggested that the observed organisms might better be considered as belonging to the Neisseria pharyngis group, rather than to a single Neisseria pharyngis sicca strain.

Summary. A case of fatal endocarditis due to a Gram-negative diplococcus of the Neisseria pharyngis group is reported. A bacteriologic and serologic study of the organism is presented.

The author wishes to thank Dr. G. P. Berry for his assistance in the preparation of this report. He wishes to acknowledge also the kindness of Dr. G. W. Rake and Dr. M. S. Shiling in furnishing strains of Neisseria pharyngis organisms for comparative study.

REFERENCES.

1. Schultz, O. T.: J. Am. Med. Assn., **71**, 1739, 1918.
2. Graef, I., de la Chapelle, C. E., and Vance, M. C.: Am. J. Path., **8**, 347, 1932.
3. Wilson, G. S., and Smith, M. M.: J. Path. and Bact., **31**, 597, 1928.
4. Wilson, S. P.: Ibid, p. 477.

A NEW METHOD OF PRODUCING HEAT IN TISSUES: THE INDUCTOTHERM.

By John R. Merriman, M.D.,

Harold J. Holmquest, B.S. (M.E.),

and

Stafford L. Osborne, B.P.E.

Chicago, Ill.

(From the Department of Physical Therapy, Northwestern University Medical School.)

A new high frequency generator, specially designed to generate heat within living tissues by electromagnetic induction, has been developed. This apparatus meets the requirements of the field of

medical diathermy. The clinical application of the Inductotherm, as this device is called, both for local treatment and the production of electropyrexia is extremely simple, requiring merely the placing of a few turns of insulated cable around or about the part to be treated. No metal electrodes are required, and burns such as those which may result from improperly applied surface electrodes are, of course, prevented.

The Inductotherm is a vacuum tube oscillator, generating an alternating current with a frequency of approximately 12,000,000 cycles per second. The current is conducted through a flexible, heavily insulated cable which is wound around or about the part to be treated. This cable may also be wound into a pancake type of coil to be placed over the tissues which it is desired to heat.

Within the coil, through which the current from the device flows, there is set up an alternating magnetic flux, having the same frequency as the current in the coil. If a conductive material is placed within the coil an electromotive force will be induced in it. As a result of this induced voltage, eddy currents of the same frequency as the exciting current will flow in the conductive material.

If living tissue is subjected to the magnetic field of the Inductotherm there will be no neuromuscular response to the eddy currents induced in the tissue, because the frequency of these currents is very high, 12,000,000 cycles per second, far above the frequencies which elicit muscular contraction.

The eddy currents induced in the more conductive materials will be the more intense, and therefore the generation of heat per unit time will be greater in these than in the less conductive materials. Obviously, if a body composed of materials of different electrical conductivities, such as tissue, for example, is placed within the coil, the intensity of the eddy currents, and consequently the heating, will be greatest in the materials of greatest conductivity. The following simple experiment will demonstrate the selective heating characteristics of high frequency currents applied in this way.

A glass vessel containing an emulsion of paraffin oil and a small amount of water rendered conductive by the addition of a small quantity of salt is placed within the coil of the Inductotherm. In a short time steam will rise from the mixture. The temperature of the mixture at this point will be considerably less than the boiling point of water, indicating that the more highly conductive globules of water have been heated more rapidly than the paraffin oil. The electrical conductivities of the water and the paraffin oil in the experiment just described may be considered roughly comparable to the electrical conductivities of vascular and adipose tissue respectively.

Experiments were conducted by two of us[1] to determine the relative heating of saline solutions of various concentrations by

high frequency currents. Curve 3, Fig. 1, represents the relative heating of these solutions by the Inductotherm. The heating of physiologic saline solution, which has a concentration of 0.85 gm. sodium chlorid per 100 gm. solution, was taken as 100% and the heating of solutions of other concentrations expressed as percentages of this degree of heating. The experimental curve deviates slightly from the theoretical straight line because of heat loss by radiation and because of the slight change in conductivity with change in temperature and in specific heat of the solution with change in concentration and temperature. For the purpose of comparison, heating curves for diathermy and a high frequency electric field are plotted in

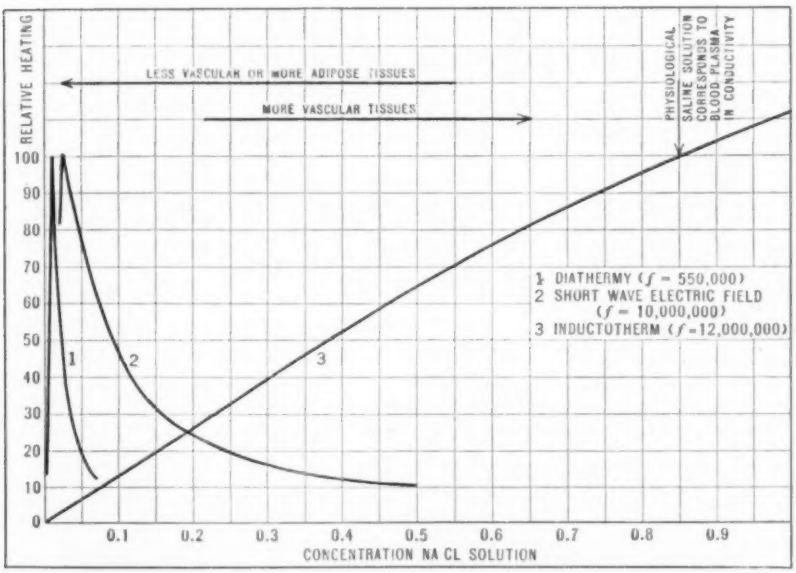

FIG. 1.—Heating characteristics of diathermy, high frequency electric fields, and the Inductotherm.

Fig. 1. Both diathermy and the alternating electric field produce maximal heating at a definite concentration. This maximal heating in each case was taken as 100% and the heating of solutions of other concentrations expressed as percentages of this degree of heating. It was observed that as the frequency of the current was increased, the point of maximal heating shifted to higher concentrations when the high frequency currents were applied by electrodes immersed in the electrolyte or by electrodes placed on opposite sides of the electrolyte with an air gap between each electrode and the electrolyte. Electrically, these two methods of application are essentially the same insofar as heating of the electrolyte is concerned, as was shown by Holmquest and Osborne.[1] It has been shown that for maximal heating

a definite relationship exists between the conductivity of the electrolyte, the dielectric constant of the electrolyte and the frequency of the current. To obtain maximal heating in an electrolyte having the conductivity of physiologic salt solution, by applying the high frequency current directly as in diathermy or by means of an electric field, it would obviously be necessary to employ a tremendously high frequency, so high in fact as to be impractical.

Physiologic saline solution has the electrical conductivity of blood plasma. As we decrease the concentration, we obtain saline solutions which correspond in electrical conductivity with less conductive materials such as blood, muscular tissue, etc., until finally we obtain a concentration electrically comparable to adipose tissue. From an inspection of the curves in Fig. 1 it is obvious that the Inductotherm alone, of the three means of heating tissue by high frequency currents, heats electrolytes in direct proportion to their electrical conductivities and hence will produce maximal heating in the most conductive tissues. The most conductive tissues are the most vascular tissues. In our opinion it is desirable to produce maximal heat in the vascular tissues rather than in the adipose tissues. The production of excessive heat in the underlying fatty tissues during the administration of high frequency currents by the usual methods is an important cause, in our opinion, of the discomfort experienced by many patients. The Inductotherm, which heats tissues in direct proportion to their conductivities, provides a means for the more comfortable treatment of patients having an unusually large amount of subcutaneous fat.

Through the courtesy of the General Electric X-ray Corporation, the Inductotherm has been used by us in animal experimentation and in the actual treatment of patients.

In all a total of 150 local treatments for arthritic joints were administered. The treatments comprised treatment of all the various joints of the body. In many cases several joints were treated simultaneously. The method of application was as described in a foregoing paragraph of this paper and illustrated in Fig. 2. The application was quickly and easily made and with no discomfort to the patient.

A total of 12 fever treatments were given by the Inductotherm. To produce fever the patient was placed in a treatment bag and two turns of the flexible cable placed around the patient and outside the bag (Fig. 3). Patients were selected so that all possible types might be represented. The weights of the patients treated ranged from 90 to 200 pounds. These patients had previously been subjected to other methods of producing fever, including hot baths, radiant heat and infra-red cabinets, electric blankets and diathermy.[2] The patients were more comfortable when the Inductotherm was used than when the other methods of raising temperature were employed. Figure 4 represents a typical 8-hr. graph of the rectal

FIG. 2.—Treatment of shoulder by Inductotherm.

FIG. 3.—Electropyrexia by the Inductotherm.

temperature, pulse and respiration of a patient in whom electropyrexia was produced by the Inducotherm.

The circulatory increase produced by the Inductotherm was observed to be great. This clinical observation is in agreement with actual measurements made by other research workers.[3] These investigators showed that the circulatory increase produced by the Inductotherm was as great as can be safely obtained by any physical means of producing artificial fever. From the data presented in their report one might draw the conclusion that no greater circulatory change can be obtained with safety by any method of producing artificial fever than was obtained with the Inductotherm. It is probably the maximal circulatory increase that it is physically possible to obtain.

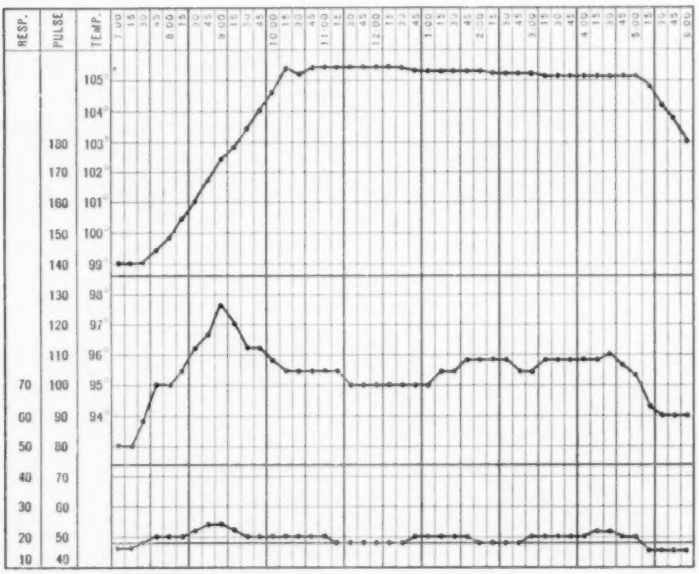

FIG. 4.—Graph of rectal temperature, pulse and respiration.

Summary. 1. A new device, the Inductotherm, for producing heat in tissues by electromagnetic induction is described.

2. Its heating characteristics are such that maximal heat is produced in the more conductive or more vascular tissues rather than in the less conductive or more adipose tissues.

3. The Inducotherm for local or general treatment requires merely the placing of a few turns of flexible insulated cable around or about the part to be treated.

4. Clinically the Inductotherm meets the requirements of the field of medical diathermy including the production of hyperpyrexia.

5. From the viewpoint of efficient heating, ease of application

and comfort of the patient, the Inductotherm in our opinion should become one of the most important clinical methods of applying heat to the tissues.

We wish to express our appreciation of the guidance and assistance of Dr. John S. Coulter, Director of the Department of Physicial Therapy, in whose department and under whose supervision this research was conducted.

REFERENCES.

1. Holmquest, H. J., and Osborne, S. L.: Heating of Electrolytes by High Frequency Currents, Delivered before Congress on Physical Therapy, Chicago, September, 1933.

2. Merriman, J. R., and Osborne, S. L.: Methods of Producing Hyperpyrexia by Various Physical Agents, Illinois Med. J., **64**, 237, 1933.

3. Johnson, C., Osborne, S. L., Scupham, G. W., and Coulter J. S.: A Clinical Study of the Effect of Hyperpyrexia on the Peripheral Circulation Reported before Chicago Society of Internal Medicine, December, 1933.

ONE HUNDRED OBESITY DIETS ON ONE CHART.

By William S. Collens, M.D.,
chief, diabetic clinic, israel zion hospital,
brooklyn, n. y.

The simplification of diet writing is an ever-pressing problem with the practising physician. Any attempt to be scientifically accurate in planning a diet for a patient is almost always attended with a degree of difficulty which requires more time and effort than most physicians can afford to give. The reason is that one who is not continuously writing diets finds it a problem to carry in his memory the carbohydrate, protein, fat and caloric values of common foods. If he carries with him a chart listing these values, he must then sit down and plan his diet on the basis of these figures. If he does not employ the method just described, then he must resort to the use of standardized diets found in most books on dietetics. Frequently he is unable to find a list of diets which is all inclusive and will meet the requirements of the individual patient under consideration.

The physician is therefore always looking for some simple method of diet writing which will obviate these difficulties and at the same time avoid tedious computations in his office practice. I described a simple chart (1) recently which was outlined to offer the practising physician a quick and ready means of arriving at a caloric diet for patients suffering from any disease necessitating the regulation of carbohydrate, protein and fat constituents. Although simple, it needs some degree of calculation and arrangement of a menu.

The present chart was devised to make available for direct reading and without any calculations whatsoever, 100 diets for cases of obesity. It is a small pocket-size folder containing two slides. The back of the chart contains the Index. One can read in the photograph the wide variety of obesity diet formulæ ranging from 600 to 1400 calories. In each caloric group there is a diversity of formulæ varying the carbohydrate, protein and fat contents. After

FIG. 1.—FRONT FACE OF OBESITY CHART.

26	27	28	DIET NO.	31	
110	60	80	Carb.	60	Grams
60	70	70	Prot.	80	Grams
13	31	22	Fat	18	Grams
800	800	800	Cal.	800	
100	50	100	BREAKFAST	50	Grams 10% Fruit
	2	1			Eggs
					Grams Cereal — cooked
	1			2	Uneeda Biscuits
30		20			Grams Bread
					cc. Cream—20%
30	30			30	cc. Milk
			LUNCH		Grams Meat, Fish or Fowl — Lean
					Grams Meat, Fish or Fowl — Fat
200	100	100			Grams 5% Vegetables
					Grams 10% Vegetables
					Grams 20% Vegetables
60	40	75		75	Grams Cheese — Low Fat
					Grams Cheese — High Fat
	2				Uneeda Biscuits
30		20		30	Grams Bread
75					Grams 10% Fruit
					Grams 15% Fruit
					cc. Cream — 20%
					cc. Milk
200	200	200		250	cc. Buttermilk
100	150	130	DINNER	120	Grams Meat, Fish or Fowl — Lean
					Grams Meat, Fish or Fowl — Fat
100	100	100		100	Grams 5% Vegetables
100					Grams 10% Vegetables
					Grams 15% Vegetables
					Grams 20% Vegetables
				75	Grams Cheese — Low Fat
					Grams Cheese — High Fat
					Uneeda Biscuits
30	20	30		30	Grams Bread
100		75			Grams 10% Fruit
					Grams 15% Fruit
					cc. Cream 20%
					cc. Milk
200	200	200		250	cc. Buttermilk

Coffee, tea, clear broth (fat free) are allowed with all meals.

Index 2

VEGETABLES—100 GRAM PORTIONS

5 per Cent

Asparagus, canned	5 tips
Asparagus, fresh	4 long stalks
Beet greens, cooked	½ cup
Celery	10 medium stalks
Cucumber	10 medium slices
Endive	10 stalks
Lettuce	10 large leaves
Mushrooms	4 medium sized
Romaine	10 large leaves
Rhubarb, cooked	¼ cup
Sauerkraut	¼ cup
Spinach	½ cup
Brussels sprouts	⅛ cup
Cabbage	1 cup
Cauliflower	¼ cup
Eggplant	1½ cups
Green pepper	1 medium
Radishes	5 small
String beans, canned	½ cup
Tomato, one	Size of egg
Watercress	2 cups
Tomato, canned	½ cup

10 per Cent

Beets	¼ cup
Green peas, canned	½ cup
Carrots	¼ cup
Olives	½ cup
Onions	6 small
Oyster plant	¼ cup
Pumpkins, canned	½ cup
Squash	½ cup
String beans, fresh	½ cup
Turnips	¼ cup

15 per Cent

Artichokes	1 medium sized
Green peas, fresh	½ cup
Lima beans, canned	½ cup
Parsnips	¼ cup

20 per Cent

Lima beans, fresh	½ cup
Navy beans	½ cup
Corn, fresh	6 tablespoons
Potatoes	2½ in. diam.

FRESH FRUITS—100 GRAM PORTIONS

10 per Cent

Orange	1 small
Grapefruit	½ small (4" diam.)
Cantaloupe	small dessert dish
Peach	1 medium sized
Pineapple	1 slice ¾ in. thick
Strawberries	¾ cup
Watermelon	1 cup
Cranberries	¾ cup
Plums	2 medium sized

15 per Cent

Grapes	18 medium
Apple	1 small sized
Apricot	2 small
Cherries	25 small
Banana	⅔ of 1 medium sized
Huckleberries	¾ cup
Blueberries	¾ cup
Raspberries	½ cup
Pear	1 small

MEATS — COOKED

100 gram portion = 4 in x 3 in. x ½ in.

Lean Meat	20% Protein, 10% Fat	Lean Fish	
Veal (Cutlet, Breast or Leg)		Pike	Mackerel
Leg of Lamb		Perch	Flounder
White Meat of Chicken		Blue Fish	Haddock
Chicken Broilers		Cod	Shrimp
Round Steak (Fat removed)		Herring	Lobster
Shoulder Steak	Tongue, fresh	Halibut	Crabmeat
Calf Liver	Beef Liver	Oysters	Clams

Fat Meat	20% Protein, 20% Fat	Fat Fish	
Lamb (Chops or Roast)		White Fish	
Beef (Roast, Sirloin, Tenderloin, Corned)		Salmon, fresh	
Pot Roast		Salmon, canned	
Tongue (Corned or Pickled)		Sardines	
Ham		Carp	
Mutton		Tunafish	
Pork (Chop, Roast)		Smoked fish	
Goose		Mackerel, salt	
Turkey		Caviar	
		Smoked halibut	
		Trout, fresh	

CEREALS—UNCOOKED

75% Carbohydrates

30 gram portions

Shredded Wheat	1
Corn Flakes	1⅓ cups
Grape Nuts	3 tablespoons
Puffed Rice	2 cups

CEREALS—COOKED

15% Carbohydrates

100 gram portions

Farina	½ cup
Macaroni	⅓ cup
Noodles	½ cup
Spaghetti	½ cup
Boiled Rice	½ cup
Oatmeal	½ cup
Hominy grits	½ cup

CHEESE

30 gram portion = 2 in. x 1 in. x ½ in.

Low Fat	High Fat
Cottage Cheese	American, Cream,
Pot Cheese	Roquefort, Swiss
Farmer Cheese	Muenster, Cheddar

Approximate Portions of Other Common Foods

Bread 4 in. x 4 in. x ½ in.	= 30 grams
Uneeda Biscuits 1	= 6 grams
Saltines 1	= 4 grams
Matzos 1 square 6 in. x 6½ in.	= 40 grams
Zwieback 2	= 15 grams

Approximate Measures

5 cc = 1 Teaspoonful
15 cc = 1 Tablespoonful
240 cc = 1 Glass

Substitutions

100 grams cooked cereal = 20 grams raw cereal
100 grams 5% vegetable = 50 grams 10% vegetable
110 grams 5% vegetable = 50 grams 15% vegetable
30 grams bread = 3 Uneeda biscuits
1 egg = 20 grams high fat cheese

OBESITY DIET CHART

Devised by WILLIAM S. COLLENS, B.S., M. D.
Israel-Zion Hospital
Brooklyn, N. Y.

COPYRIGHT 1933
BY
FORM PUBLISHING CO.
"Printed Forms for the Doctor"
200 Hudson St., New York City PRICE 50 Cents

FIG. 2.—BACK FACE OF OBESITY CHART.

INDEX TO OBESITY DIET FORMULAE

are allowed with all meals.

Turkey

Trout, fresh

FIG. 2.—BACK FACE OF OBESITY CHART.

INDEX TO OBESITY DIET FORMULAE

INDEX 1

Diet No.	Carb. grams	Prot. grams	Fat grams
	600 CALORIES		
1	30	30	40
2	50	30	30
3	40	40	30
4	50	50	22
	700 CALORIES		
5	40	40	42
6	50	40	38
7	60	40	33
8	40	50	38
9	50	50	33
10	60	50	29
11	75	50	22
12	90	50	16
13	50	60	29
14	60	60	24
15	75	60	18
	800 CALORIES		
16	40	40	53
17	50	40	49
18	50	50	44
19	70	50	35
20	90	50	27
21	110	50	18
22	50	60	40
23	60	60	35
24	70	60	31
25	90	60	22

INDEX 2

Diet No.	Carb. grams	Prot. grams	Fat grams
	800 CONT.		
26	110	60	13
27	60	70	31
28	80	70	22
29	100	70	13
30	60	80	27
31	80	80	18
	900 CALORIES		
32	70	40	50
33	90	40	42
34	50	60	50
35	70	60	42
36	90	60	33
37	110	60	24
38	40	80	47
39	60	80	38
40	80	80	29
41	100	80	20
42	40	100	38
43	60	100	29
44	80	100	20
	1000 CALORIES		
45	70	40	62
46	90	40	53
47	110	40	44
48	60	50	62
49	80	50	53
50	100	50	44

INDEX 3

Diet No.	Carb. grams	Prot. grams	Fat grams
	1000 CONT.		
51	125	50	33
52	150	50	22
53	60	60	58
54	75	60	51
55	90	60	44
56	110	60	36
57	125	60	29
58	150	60	17
59	50	70	58
60	70	70	49
61	90	70	40
62	110	70	31
63	125	70	24
64	60	80	49
65	80	80	40
66	100	80	31
67	40	100	49
68	60	100	40
69	80	100	31
70	100	100	22
	1200 CALORIES		
71	80	60	71
72	100	60	62
73	120	60	53
74	60	80	71
75	80	80	62

INDEX 4

Diet No.	Carb. grams	Prot. grams	Fat grams
	1200 CONT.		
76	100	80	53
77	120	80	44
78	60	100	62
79	80	100	53
80	100	100	44
81	120	100	36
82	80	120	44
83	100	120	36
	1400 CALORIES		
84	80	60	93
85	100	60	84
86	120	60	75
87	80	80	84
88	100	80	75
89	120	80	67
90	80	100	75
91	100	100	67
92	120	100	58
93	150	100	45
94	80	120	67
95	100	120	58
96	120	120	49
97	150	120	36
98	80	150	53
99	100	150	45
100	120	150	36

DIRECTIONS:—Select in the table above the calories and formula you wish to give the patient. Then note the Diet Number to the left of the formula and the Index Number at the top of the column. Withdraw that Index card and reinsert so that the figures can be read through the window on the front face of the chart. When the Diet Number is seen in the window, read the menu for each meal. Substitution tables are found to the right of the window.

selecting the formula for the patient under consideration, the Diet Number to the left of the formula and the Index Number at the top of the column are noted. The Index is then withdrawn and reinserted so that the figures are visible through the window on the front face of the chart (Fig. 1). When the Diet Number appears in the window, the menu for the selected formula appears at the same time and can be read directly for each meal.

For Example. Suppose you wish to give a patient a diet containing 800 Calories. You can then select one of 16 diets listed for 800 Calories. If you choose a diet containing C 80, P 80, F 18, you will observe this to be Diet No. 31, Index No. 2. Withdraw Index No. 2 from the folder and reinsert so that Index No. 2 faces the window (see photograph of Front Face of chart).

The menu is then read directly as follows:

Breakfast: 50 grams 10% fruit
2 Uneeda biscuits
30 cc. milk

Lunch: 75 grams cheese, low fat
30 grams bread
250 cc. buttermilk

Dinner: 120 grams meat, fish or fowl, lean
100 grams 5% vegetables
75 grams cheese, low fat
30 grams bread
250 cc. buttermilk

Coffee, tea, clear broth (fat-free) allowed with all meals.

A large list of substitution tables is presented on the Front Face of the chart which makes it possible to translate the weighed portions listed into approximate household measures.

The food values employed in preparing this menu chart are based upon average figures obtained from Bradley's Tables of Food Values.[2] The list of common foods from which these menus have been computed is as follows:

	Percentage carbohydrate.	Percentage protein.	Percentage fat.
Bread	50	10	
Buttermilk	5	3	0.5
Cereal, cooked	15	3	
Cheese, low fat	4	21	1
Cheese, high fat	..	30	35
Cream, 20%	4	3	20
Eggs (1)	..	6	6
Fruit, 10%	8	0.5	
Fruit, 15%	15	1	
Meat, fish or fowl, lean	..	20	10
Meat, fish or fowl, fat		20	20
Milk	5	3	4
Vegetables, 5%	4	1	
Vegetables, 10%	8	2	
Uneeda biscuits (1)	5	0.5	

Summary. A diet chart is presented which makes it possible to read the menu directly, without calculation, for almost any reduction diet a physician may wish to prescribe.

NOTE.—I wish to thank Miss Rose Kay for her assistance in preparing these diets.

BIBLIOGRAPHY.

1. Collens, W. S.: A Simple Method for Writing a Scientific Diet, J. Am. Med. Assn., **100**, 184, 1933.
2. Bradley, A. V.: Tables of Food Values, Manual Arts Press, Peoria, Illinois, 1931.

SYMPTOMATIC RELIEF OF EMPHYSEMA BY AN ABDOMINAL BELT.*

BY H. L. ALEXANDER, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE; ASSOCIATE PHYSICIAN TO THE BARNES HOSPITAL,
AND
W. B. KOUNTZ, M.D.,
INSTRUCTOR IN MEDICINE, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE; ASSISTANT PHYSICIAN TO THE BARNES HOSPITAL, ST. LOUIS, MO.

(From the Department of Internal Medicine, Washington University Medical School and the Barnes Hospital, St. Louis, Mo.)

IN obstructive emphysema, particularly in advanced cases, difficulty in breathing is due largely to mechanical factors. The voluminous lungs hold the diaphragm in the position of inspiration so that it can contract little, if at all. The chest is expanded to a barrel shape and further distention is limited no matter how great the respiratory effort. As these processes develop, there is a gradual reduction in the vital capacity of the lungs which at times reaches a point wherein the patient is totally disabled. The respiratory demands of even slight exertion cannot be met without distress.

The problem of facilitating breathing in emphysematous individuals by correcting mechanical defects, received considerable attention, especially in Germany, some 20 years ago. Various operative procedures and mechanical devices were advocated. Severance of costal cartilages in order to relieve intrathoracic pressure was recommended by Freund[1] and by Seidel.[2] Different types of apparatus were used, particularly pneumatic cabinets.[3] One was so regulated that compressed air encompassed the body during expiration so that a larger inspiratory excursion became possible. Another (the Waldenburg apparatus) could be regulated so that the patient inspired outer air but exhaled into rarified air, a procedure designed to reduce lung volume. The Bruns apparatus was of a similar nature but cheaper and more easily handled. The

* Read in abstract form before the 48th Meeting of the Association of American Physicians, Washington, D. C., May 9, 1933.

Rossbach breathing chair and the Boghean breathing machine were mechanical instruments in which the patient was placed and the abdomen compressed during expiration. The Hofbauer apparatus carried out this process more simply. It consisted of a bag placed around the abdomen and attached to a tank of compressed air. A timing device permitted the bag to fill wi' air during each expiration. As a result abdominal compression was transmitted to the thorax and air was thus expelled from the lungs.

Breathing exercises and manual compression of the thorax for a period each day by a masseur were measures also recommended to overcome the mechanical handicaps to breathing in emphysematous individuals. Most of these procedures were either too cumbersome to be of use or not sufficiently effective to be generally adopted.

The observation that patients with advanced emphysema assume positions which compress the abdomen (leaning forward in the sitting posture, squatting on the haunches, tightening the belt) led to the development of the belt herein described. It was inferred that the increased intraäbdominal pressure thus created was transmitted against the flattened diaphragm which would then be pushed upward toward its normal expiratory position. From that position excursion would again be possible. To confirm this supposition a patient was stood before the fluoroscope. An orthodiagram was made of the flattened diaphragm. As pressure was then exerted with the flat of the hand just above the symphysis pubis, the diaphragm rose and began to assume its normal dome shape. On deep inspiration the diaphragm descended and the patient stated that he was again getting air into his lungs (Fig. 1).

To maintain the diaphragm in its elevated position, a belt was devised. This is made of canvas and fits around the lower abdomen so that its lower edge rides just above the symphysis pubis. The upper edge comes well below the umbilicus. Just above the symphysis a leather or soft sponge rubber pad is fitted. This is suspended to the upper border of the belt by a band of spring steel, so bent that pressure is exerted inward and upward toward the promontory of the sacrum. The pad is 3 inches high, 5 inches wide and 1 inch thick. These measurements are approximate and vary with the size and habitus of the patient. The pressure of the pad against the abdomen varies according to posture. It is increased on sitting or bending forward, and lessened in the standing and reclining positions. These variations are obvious to the patient in that the belt feels too tight or too loose. To maintain a constant and comfortable pressure, a screw bolt in contact with the anterior face of the pad projects through the front of the belt. The patient can easily adjust the pressure by a turn or two of the screw head (Figs. 2, 3 and 4). The belt laces in the back and has thin round white rubber thigh straps. It is applicable to all but emaciated patients with sunken abdomens where there is little resistance to "press against."

Twenty-five patients with obstructive emphysema were fitted with abdominal belts. An orthodiagram and vital capacity determination before and after application were made in each case. With the exceptions noted in Table 1, these patients were kept under observations for periods varying between 2 and 6 months.

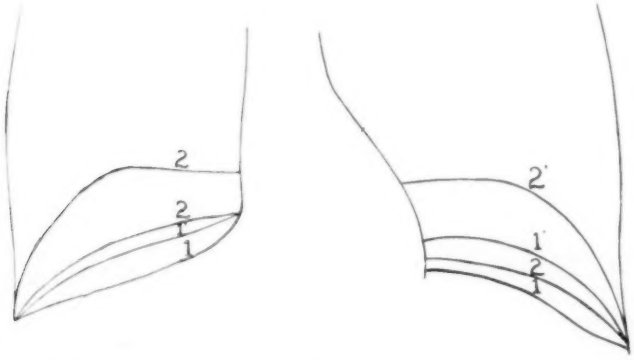

FIG. 1.—Orthodiagram of diaphragmatic positions in a patient with obstructive emphysema. 1′, Expiration; 1, extreme inspiration; 2′, expiration during abdominal pressure; 2, extreme inspiration during abdominal pressure.

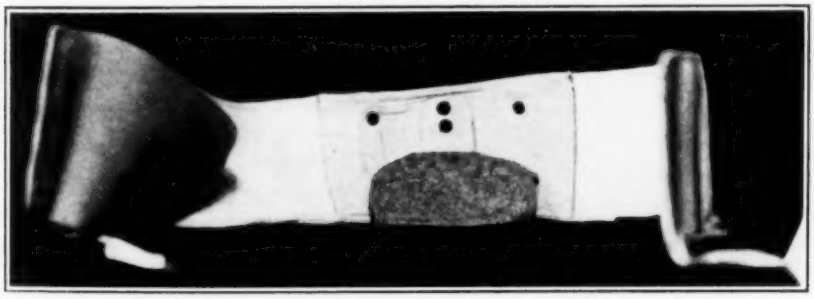

FIG. 2.—Inner face of belt, showing the pad. The 2 rivets vertically arranged are holding the spring steel to which the pad is attached.

Two patients whose vital capacities were increased could not or would not wear the belt. Four patients (1 with Ayerza's disease) after a fair trial maintained that the belt did not help them. The remaining 19 reported distinct subjective improvement. The average increase in vital capacity for the entire group was 39%. Of interest is the observation that the 1 patient who has worn the belt as long as 6 months has a restoration of excursion of his diaphragm even when the belt is not worn.

Intrapleural pressures were taken on a few patients before and after application of the belt. Similar pressure readings were made with the belt loosely in place and after it had been tightened. In

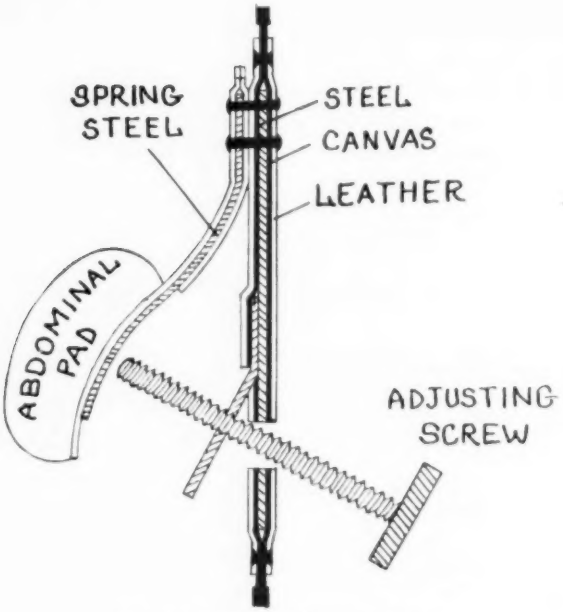

FIG. 3.—Schematic drawing of belt.

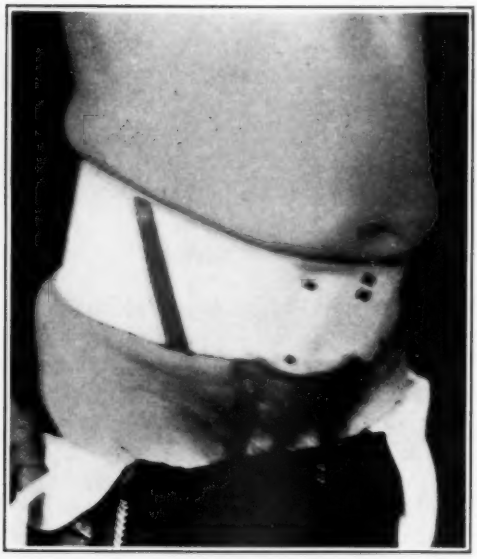

FIG. 4.—The belt in place. The screw head projects at the lower border in line with the 2 vertical rivets.

each instance the characteristically elevated intrapleural pressure of obstructive emphysema became *more negative* with the belt applied. For instance, expiratory and inspiratory values of +1 cm. of water and −3 cm. respectively, without the belt, became −2 cm. and −8 cm. with the belt in place. This effect is attributed to the fact that intrapleural pressure is influenced by the extent of respiratory excursion and thus falls as diaphragmatic movement becomes restored.

TABLE 1.—INCREASE IN VITAL CAPACITY AND SYMPTOMATIC IMPROVEMENT IN PATIENTS WITH EMPHYSEMA AFTER APPLICATION OF BELT.

Patient No.	Etiology of emphysema.	Vital capacity. Before belt, cc.	Vital capacity. With belt, cc.	Per cent increase.	Remarks.
1	Bronchitis	1800	3200	77	Improved.
2	Bronchitis	2500	3300	32	Improved.
3	Asthma	1400	2200	57	Unable to wear belt.
4	Bronchitis	2200	3300	50	Improved.
5	Influenza	2500	3500	40	Improved.
6	Asthma	1700	2500	47	Would not wear belt.
7	Asthma	2500	3200	28	Improved.*
8	Bronchitis	3000	3700	23	Improved.*
9	Pulmonary sclerosis	1000	1400	40	No improvement.
10	Bronchitis	2900	3600	24	Improved.
11	Bronchitis	2400	3300	37	Improved.
12	Asthma	2250	3700	64	Improved.
13	Bronchitis	1500	2500	66	Improved.
14	Indeterminate	2250	2800	24	Improved.
15	Influenza	3500	4200	20	Improved.
16	Bronchitis	1100	1900	72	No improvement.
17	Bronchitis	2800	3600	28	Improved.
18	Bronchitis	2000	3100	55	Improved.
19	Asthma	2200	3100	40	Improved.
20	Bronchitis	1800	2600	44	Improved.
21	Bronchiectasis	2900	4000	37	Improved.
22	Bronchiectasis	2400	3400	41	Improved.
23	Bronchiectasis	2600	3200	23	Improved ?
24	Asthma	1100	1200	9	Improved.
25	Asthma	1600	1600	0	No improvement.

* Did not return for further observation.

We observed no bad effects on the digestive system by wearing the belt. As a matter of fact, many of these patients with emphysema have a visceroptosis due perhaps to the pushing down of the viscera by the flattened diaphragm. Some of these patients said their abdomen felt better, but we have made no statistical observations on this point.

Summary. In advanced obstructive emphysema, difficulty in breathing is due principally to mechanical factors. The large lungs hold the diaphragm in the position of inspiration, and indirectly they also distend the chest to a barrel shape. Respiratory excursion is thereby limited.

It has been found that the diaphragm can be pushed upward toward its expiratory position by means of abdominal pressure, properly applied. From this position contraction again occurs.

In order to maintain adequate intraabdominal pressure, a belt has been devised. In a series of 25 patients with advanced obstructive emphysema to whom belts have been fitted, 19 have been subjectively improved. The average increase in the vital capacity of the lungs has been 39%.

With improvement in respiratory function, the characteristically elevated intrapleural pressure of obstructive emphysema has been found to become more negative and thus approach more normal values.

REFERENCES.

1. Freund, W. A.: Zur operativen Behandlung gewisser Lungenkrankheiten, inbesondere des auf starrer Thoraxdilatation beruhenden alveolären Emphysems, Ztschr. f. exp. Path. u. Therap., **3**, 479, 1906.

2. Seidel, H.: Bemerkungen zur Chrondrektomie bei Emphysem infolge starrer Thoraxdilatation, Beitr. z. klin. Chir., **58**, 808, 1908.

3. Staehelin, R.: Handbuch der inneren Medizin, 2d ed., Berlin, Julius Springer, **2**, 1690, 1930.

THE MECHANISM AND USE OF ABDOMINAL SUPPORTS AND THE TREATMENT OF PULMONARY DISEASES.*

By Burgess Gordon, M.D.,
PHILADELPHIA.

(From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital, and the White Haven Sanatorium.)

In previous reports[1,2] it was shown that a decrease in pulmonary manifestations occurred in 2 tuberculous patients with enlargement of the abdomen. This improvement was attributed in part to the effects of diaphragm elevation favoring rest for the affected lungs. The first case was a pregnant woman with artificial pneumothorax on the left side. During gestation an elevation of the diaphragm occurred with an increase of pressure in the left pleural cavity, a shift of the heart to the right and a relative increase in "thoracic type" of breathing, indicating that the compression due to diaphragm elevation was considerable. After delivery the diaphragm excursions returned to lower levels, as in phrenicectomy cases following a regeneration of the phrenic nerve. This suggested that the sudden shift of the diaphragm, resulting in a preponderance of "abdominal type" of breathing, might explain certain instances of activity of tuberculosis following pregnancy. The second patient had enlargement of the liver and ascites. With the

* Read before a meeting of the Section of General Medicine of the College of Physicians of Philadelphia, Philadelphia, November 27, 1933.

gradual increase in the abdomen there was a corresponding elevation of the diaphragm and decrease in fatigue, dyspnea, cough and expectoration. As observed in the first case the pulmonary features were such as would be expected in bilateral phrenicectomy.

It was pointed out in the discussion of these patients that diaphragm elevation could be obtained by using abdominal supports. This suggested a means for preventing the spread of tuberculosis following pregnancy. It was suggested further that the mechanism may be applicable for the treatment of chronic pulmonary diseases in which dyspnea and difficult expectoration were prominent features. To obtain further information on possible indications an evaluation of standard treatment was undertaken. This was intended especially to throw light on the rôle of mechanical factors in tuberculosis. Certain data and impressions have been incorporated in the present paper.

It is obvious that rest, nutritious diet and the patient's coöperative attitude are the most important influences in the treatment of pulmonary tuberculosis. Although physical characteristics may not be determining factors, it is perhaps true that thin individuals offer the least favorable prognosis. Artificial pneumothorax, phrenicectomy and thoracoplasty, used as supplementary measures in selected cases, have definite value due evidently to limitation of motion of the affected lung. The failures that occur following all types of treatment—even when the outlook has been encouraging—may be attributed to delays in discarding some measure or in adopting radical procedures. The indications for artificial pneumothorax are debated widely; some believe that it should be employed at the beginning even in early cases, others consider that its value has been overemphasized. This is equally true of thoracoplasty. Surgeons want cases that are not far advanced, while internists wish to delay operation until conservative measures have failed, admitting that later the prospects for satisfactory surgery are remote.

From such considerations it seemed as if some fundamental mechanism had perhaps been omitted. That this may account for certain failures in all forms of treatment seemed possible because of the occasional unexpected return or exaggeration of symptoms which apparently had been controlled. Deep and not well coördinated movements of the diaphragm as evidenced by racking cough and feeble abdominal type of breathing were considered part of this uncontrolled mechanism.

Although the rest-dietetic régime is helpful in the management of pulmonary abscess and bronchiectasis, the results are not to be compared with its general value in pulmonary tuberculosis. This is due largely to the fact that suppurative conditions generally have disturbing systemic effects, as may be appreciated in comparing the clinical picture of tuberculosis with one of equal involvement of

bronchiectasis. In the latter there is in addition to loss of appetite, weight, strength, and elevated temperature the appearance of an extremely "toxic" state. Here perhaps the most successful of surgical measures is bronchoscopic drainage. Even when it fails as a cure, there is at least transient relief; but in order to obtain the greatest benefit bronchoscopy should be done 2 or 3 times weekly. In the majority of instances collapse measures are unsatisfactory, the least desirable results being obtained in artificial pneumothorax, the most favorable in phrenicectomy. The value of external drainage of lung abscess adjoining the chest wall is well recognized. In lobectomy, with new developments in technique, there may be a promising future for bronchiectasis. As a medical procedure so-called postural drainage may have definite value; success depends largely on the patient's coöperation and selection of the proper posture.

Various influences have been mentioned to explain the failures of collapse treatment in pulmonary abscess and bronchiectasis. Of these the marked sensitivity of the lungs to necrotic tissue products and interference with drainage due to compression of the bronchi have been noted. This occurs frequently in the use of artificial pneumothorax. A further disturbance may occur in phrenicectomy cases due to a loss in the expulsive force of the diaphragm.

The value of drugs in all forms of chronic pulmonary disease is debated widely; at best, the effects are symptomatic and often followed by disturbing manifestations. This is especially true in the use of opium derivatives in stopping cough, but with retention of secretion or with expectorants, where not infrequently gastro-intestinal symptoms follow.

It seems fair to conclude, then, that the indications for using mechanical measures in pulmonary diseases are as important as the contraindications. This is emphasized in the favorable results that may be obtained from collapse therapy in pulmonary tuberculosis, and the harm that may result in suppuration. In order to obtain further data on the subject of mechanical influences measurements were obtained of the chest, diaphragm and abdominal movements during normal and forced respirations. The subjects were of different weight levels and had various respiratory diseases and stages. The excursions of the diaphragm were studied with a marked fluoroscopic screen and the chest and abdominal movements were studied by means of silhouettes taken with the individual and camera in fixed positions. Differences in expansion and contraction of the chest and abdomen were calculated from a graph superimposed over the negatives when the photographs were developed.

Measurements in Obese Patients. In both men and women there was usually a greater degree of thoracic than abdominal expansion. This was less striking in the pendulous abdomen than in the rotund

muscular form. Thoracic movements were relatively greater in the "athletic" type with broad shoulders and "well developed" chest. The diaphragm levels were usually lowest in the standing posture, especially in the patient with a relaxed pendulous abdomen. In all types the abdominal movements increased during sleep and relaxation. During cough the indrawing of the abdomen was limited almost entirely to the upper third and in some cases was scarcely perceptible.

Measurements in Malnutrition. In both men and women with progressive loss of weight there was usually a preponderance of the abdominal type of breathing, especially in the long, flat type of chest and scaphoid abdomen. During cough there was a marked general retraction of the abdominal wall followed by rapid expansion; the latter occurring with the sudden rebound of the diaphragm in deep inspiration. The excursions of the diaphragm during cough showed in several instances a higher level at the end of forceful expiration and a lower level during the next inspiration than would be expected in well-nourished individuals. These phenomena were exaggerated in advanced pulmonary diseases especially the preponderance of abdominal type of breathing. In patients with marked emphysema the "flattened" diaphragm, as reported previously by Alexander and Kountz,[3] was a feature.

Since there is usually a preponderance of "abdominal" breathing in pulmonary disease and relatively greater "thoracic" breathing in well-nourished and well-developed individuals it seemed of interest to study the effects of limiting lung motion in the verticle plane.

Principle of Abdominal Support. Accordingly a number of abdominal supports were devised and tried. Two principles were used: one to limit the expansion of the abdomen, the other to exert pressure from below upward on the abdomen and its contents. The problem was simplified in the subject with a large, well-developed type of abdomen. In this a suspensory model, consisting of a front piece made of heavy broadcloth cut somewhat diamond shaped and equipped with stays, buckles, straps and a back piece was entirely satisfactory. For individuals with less abdominal fat the stays in the front piece were bent and the concavity placed in apposition to the abdominal wall. In patients with large, relaxed pendulous abdomens, it was necessary to "tuck," as well as compress, the fat. For this purpose a support was constructed from an aluminum plate 8 cm. in width and 12 cm. in length. A pad of slightly smaller dimensions was attached to the under surface of the plate. The support is held in position by three sets of leather straps, buckles and a "form fitting" back. The proper adjustment is evident when rolls of fat rise above the borders of the plate and abdominal movements are not visible. In patients requiring considerable pressure over the abdomen, especially bed patients with dyspnea and ambulatory cases with bronchiectasis and considerable cough, a different design was found necessary. Fundamentally the same feature of compression was used but instead of "binder" construction, which causes approximately the same degree of pressure on all sides of the abdomen, the principle of central pressure was employed. The device consists of an aluminum plate somewhat the shape of a four-leaf clover, approximately 10 by 12 cm. in

diameter, enclosed in leather and cloth.* Two tension springs 22 to 28 cm. in length covered with canvas which project at both ends in the form of straps pass over the aluminum plate at the upper and lower margins. These are curved slightly at the ends so as to follow the surface of the waist and hips. The straps are fastened to buckles attached to the back piece. Compression is obtained by bending the springs and tightening the straps (Fig. 1). A single spring fastened to the lower third of the support is sufficient for patients with moderate development of the abdomen.

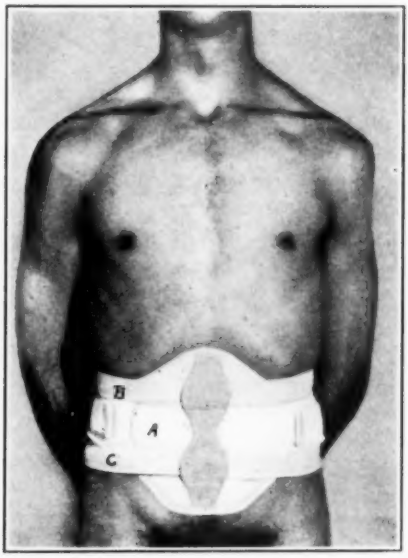

FIG. 1.—Type of abdominal support used for inducing considerable pressure over the abdomen. It consists of an aluminum plate "A" covered with cloth and leather and 2 steel springs terminating in tapes "B" and "C," which are adjusted to buckles on the back piece.

The abdominal supports were used in a group of 41 patients, with various pulmonary diseases, who had been on standard treatment for more than 6 months. Some patients had been observed for more than 4 years. The group includes: bronchiectasis, 6; so-called simple bronchitis, 2; chronic bronchitis and emphysema, 4; pneumoconiosis, 7; bronchial asthma with chronic bronchitis and emphysema, 4; pulmonary tuberculosis with considerable fibrosis, 18. There was no change in treatment except to increase exercise or discontinue unimportant procedures. In most instances the supports were worn day and night. All the patients were studied by Roentgen ray and anatomical measurements as in the preliminary studies and in a few instances vital capacity determinations were made. The occurrence of symptoms such as dyspnea, cough and the type and amount of expectoration were noted.

The immediate effects obtained from the use of abdominal sup-

* These supports were developed with the assistance of Mr. J. J. Amsterdam, and Mr. R. K. Sennig, of Amsterdam Brothers, Inc., Philadelphia.

FIG. 2 *A*.—A drawing constructed on graph paper from the accompanying silhouette. The patient had moderately advanced tuberculosis and pneumoconiosis. The diaphragm level at full inspiration was calculated from the roentgenogram shown in Fig. 3 *B*, lines *B*. The elevation is designated as 53 mm. counted on the graph.

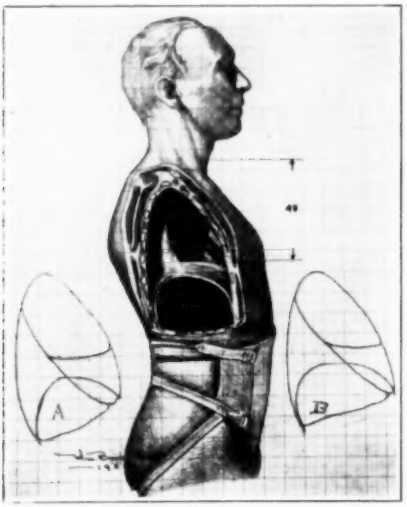

FIG. 2 *B*.—Drawing constructed from the silhouette of the same individual (2 *A*), wearing a diamond-shaped abdominal support with steel stays. The diaphragm level at full inspiration was calculated from the roentgenogram shown in Fig. 3 *A*, the level being designated as 49 mm. counted on the graph. A comparison with 2 *A* will show a decrease in the transverse diameter of the abdomen and an increase in the diameter of the thorax. The changes in lung volume are illustrated in diagram *B*. In comparing this with diagram *A* (Fig. 2 *B*) the increase in the transverse dimensions of the lungs and the decrease in vertical dimensions are shown.

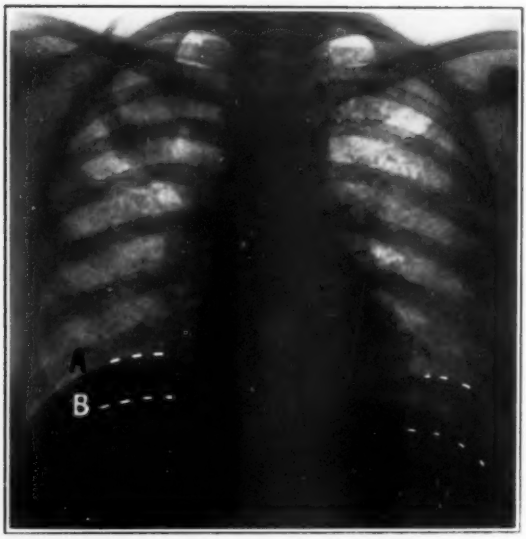

FIG. 3 *A*.—Roentgenogram of the same individual in full inspiration while wearing an abdominal support. The dotted lines "A" indicate the level of the diaphragm. Dotted lines "B" were obtained by superimposing Fig. 3 *B* over the roentgenogram and tracing the level of the diaphragm.

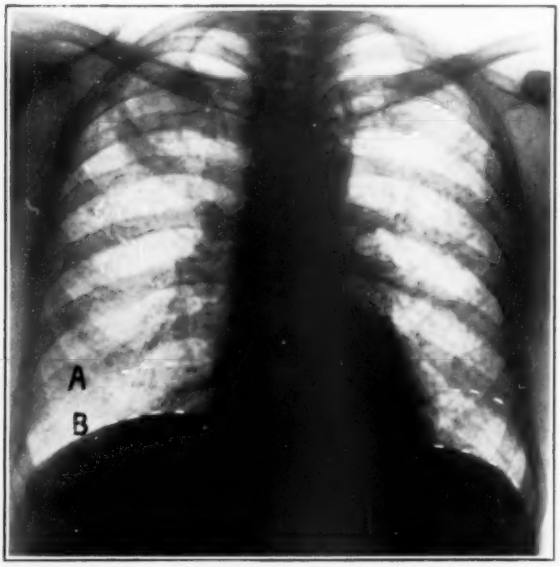

FIG. 3 *B*.—Roentgenogram of the same individual in full inspiration without an abdominal support. Dotted lines "A" show the level of the diaphragm which corresponds with "A" in Fig. 3 *A*. Dotted lines "B" show the level of the diaphragm without the use of an abdominal support and correspond with "B" in Fig 3 *A*. The elevation was 2.5 cm.

TABLE 1.—THE EFFECTS (IMMEDIATE) OF ABDOMINAL SUPPORTS IN VARIOUS PULMONARY DISEASES.

Patient	Diagnosis.	Symptoms without support.	Effects after wearing support.
H. O.	Pneumoconiosis	Marked dyspnea; cough and expectoration	Breathes easily; cough and expectoration decreased (expectoration marked at first); formerly in bed; now 1 hour exercise; support worn 3 weeks.
J. B.	Pneumoconiosis	Marked dyspnea; cough and expectoration	Dyspnea and cough decreased; expectoration increased first 2 weeks, then decreased; formerly on cure only; now 1 hour exercise; support worn 3 weeks.
H. C.	Pneumoconiosis	Practically invalid; cyanosis; marked dyspnea; cough and expectoration; pain in chest and abdomen	Striking general improvement; cyanosis and dyspnea decreased; cough appears "higher" in chest and more productive; no pain; formerly in bed; now on cure and short exercise; support worn 4 weeks.
M. B.	Pul. tuberculosis (far adv.)	Dyspnea and cough; loss of weight	Dyspnea and cough decreased; gain in weight; formerly in bed; now on cure and 1 hour exercise; support worn 3 weeks.
J. L.	Pul. tuberculosis (far adv.)	Heavy breathing; cough and expectoration; weakness	Breathing "more with chest and easier;" cough less frequent; expectoration reduced, strength increased; formerly in bed; now on cure and ½ hour exercise; support worn 3 weeks.
P. S.	Pul. tuberculosis (mod. adv.)	Cough and expectoration; "breathes heavily" on walking up a slight grade	Breathes easily at all times; cough and expectoration decreased; formerly on cure and 15 minutes exercise; now all-day cure and 1 hour exercise; support worn 4 weeks.
F. L.	Pul. tuberculosis (mod. adv.)	Cough and expectoration; "breathes heavily"	Breathes easily; cough less frequent; each cough more productive; formerly on cure; now on 1 hour exercise; support worn 4 weeks.
C. K.	Pul. tuberculosis	Dyspnea; weakness; loss of weight	Dyspnea decreased; increased strength and weight; in bed; support worn 7 weeks.
A. C.	Pul. tuberculosis (far adv.)	Dysphea; cough and expectoration	Dyspnea less; increased thoracic movements; cough infrequent; each cough more productive; formerly in bed; now on cure and 1 hour exercise; support worn 5 weeks.
J. C.	Pul. tuberculosis (far adv.); pneumoconiosis	Marked dyspnea; weakness; difficult expectoration; severe cough	Striking effects within 3 hours after support was applied; comfortable on lying flat in bed; formerly 4 pillows were necessary; expectoration facilitated and racking cough stopped; general appearance strikingly improved.
G. H.	Bronchiectasis (dur., 3 years)	Dyspnea and cough; foul expectoration and weakness; loss of weight	No dyspnea on walking; cough and expectoration decreased; sputum not foul; marked increase in strength; gain in weight; support worn 2 weeks.
G. V.	Bronchiectasis (dur., 9 years)	Dyspnea and cough; profuse expectoration; weakness; pain in abdomen	Dyspnea less; no pain; cough less frequent and more effective in raising sputum; strength increased; support worn 2 weeks.
C. W.	Bronchiectasis (dur., 5 years)	Dyspnea on walking; paroxysmal dyspnea; cough and expectoration; loss of weight	Striking general improvement; dyspnea decreased; no paroxysmal attacks; expectoration and cough decreased; 4 kg. gain in weight; can walk easily without dyspnea; support worn 4 weeks.
A. S.	Bronchiectasis (dur., 4 years)	Dyspnea; racking cough; difficult expectoration	Breathes more easily; expectoration facilitated; support worn 6 weeks.
H. M.	Bronchiectasis (dur., 7 years)	Dyspnea; cough; difficult expectoration; pain in abdomen	Dyspnea decreased; expectoration facilitated; pain in abdomen due to former racking cough stopped; support worn 3 weeks.
H. W.	Bron. asthma; ch. bronchitis; emphysema (dur., 6 years)	Marked dyspnea; paroxysmal dyspnea and cough; pain in abdomen	Striking general improvement; dyspnea decreased; attacks less frequent; cough less severe; support worn 6 months; died suddenly from coronary thrombosis; aged 69.
V. Mc.	Bron. asthma; ch. bronchitis; emphysema (dur., 4 years)	Cough and expectoration; dyspnea on exertion; pain in abdomen	Cough and expectoration decreased markedly; no dyspnea on walking; all-day cure and exercise; support worn 2 weeks.
G. E.	Ch. bronchitis; emphysema (dur., 7 years; glassblower, 21 years)	Dyspnea, especially lying on left side; "difficulty in releasing air;" paroxysmal dyspnea; cough	Dyspnea and cough decreased markedly; can lie on left side; support worn 1 week.

ports in 18 patients are shown in the accompanying table. In the remaining number the results were inconstant and tabulation was not attempted. Discomfort occurred in 4 thin patients; there was some question of extension in 3 tuberculous patients and the supports were removed. Of special interest is the decrease of dyspnea, cough, expectoration, fatigue and pain in the abdomen. This was striking in patients with severe racking cough and difficult expectoration. In some instances the improvement was reflected in expressions of comfort on the face. Exercise was started or increased in patients who experienced marked symptomatic relief. This occurred without discomfort and usually a request was made for additional exercise. Objectively there was a definite limitation in the expansion of the abdomen and a relative increase in the horizontal movements of the thorax. This was less marked in bed patients. In a few instances a striking reduction in the number of coarse râles in the lungs was noted. The roentgenogram of the chest showed elevations of the diaphragm varying from 1 to 3.5 cm.; the excursions were usually limited in extent (Figs. 2A and B; 3A and B). Especially striking was the decrease in the upward "rush" and "rebound" of the diaphragm in uncontrolled inspiration and expiration as in cough. Several roentgenograms indicated decreased illumination of the lungs. The vital capacity determinations showed a reduction from 5 to 20%. After the supports were worn for a few days the percentage returned to within 5 to 10 points of the original figure. This suggested that the breathing space in the lungs was reduced at first as a result of compression from the diaphragm and later increased as a result of greater thoracic expansion. No attempt was made to evaluate the changes in the lungs *per se* since a larger group should be studied critically over a long period of time. It is merely noted that in 4 tuberculous patients one large cavity disappeared and three decreased more than 2 cm. in diameter.

The present study indicates that abdominal supports may be useful for the relief of symptoms in various pulmonary diseases. In a number of instances, the results were more striking than would occur ordinarily from the use of "anti-spasmodic" and "expectorant" drugs. Although the effects of healing were not considered, the impression was received in certain tuberculous patients that the processes had become quiescent. This was suggested chiefly because in spite of exercise there was an increase in strength and gain in weight. However this may be regarded as an index of abeyance, there was no doubt that certain patients "carried" their infections with less general disturbance.

Various explanations for the findings may be considered. These are: that the elevated and restricted motion of the diaphragm favors rest for the lungs by distributing lung excursions somewhat evenly over different planes; the mechanism of breathing is effectively regulated due to improved coördination between diaphragm and thoracic movements; the "cushioning" effect from the secure abdom-

inal wall prevents a sudden "rebound" of the diaphragm following cough and thus reduces lung trauma; the long upward "rush" of the diaphragm due to negative pleural pressure is reduced; the removal of diseased tissue products, especially from the basal areas of the lungs is facilitated. In considering the mechanism of diaphragm elevation an illustrative comparison may be made between a perfect automobile inner tube and one with an area of thin rubber. On filling, the expansion of the perfect tube is approximately equal throughout. With the imperfect tube there is a "bulge" in the area of thin rubber. This appears before stretching occurs in other parts. In forcing air from the tube by compression the imperfect part will swell, as occurred in filling, which delays the passage of air. These features are comparable with the diseased lung as to its emptying and filling efficiency. In the patient with loss of weight or relaxed pendulous abdomen, the diaphragm is lowered and perhaps weakened. Furthermore the excursions are not well coördinated. This favors retention of air and secretions in the dependent parts of the lungs. An additional factor occurs in advanced basal disease, especially emphysema, in which the accessory muscles of the thorax play an important part in expiration. This tends to hold the diaphragm in a "flattened" position and the air and secretions are "locked" in the bases of the lungs. The inefficiency of the diaphragm is shown in its failure to compress the lungs from below upward. This corresponds with the "bulge" mentioned in the parallel drawn of the thinned area of the rubber tubing. Whereas the diaphragm is normally vigorous in function, it becomes in malnutrition and pulmonary disease a relatively weak and inefficient structure. Dr. McCrae's[4] use for many years of abdominal binders to reduce the discomfort in whooping cough supports the thesis of this study. Furthermore, patients with extreme dyspnea have discovered that comfort is obtained in the sitting posture with the body bent over the knees. These observations are similar to the observation of Alexander and Kountz[3] that 1 of their patients with emphysema breathed more easily when resting on his hands and knees or when wearing an abdominal support. These effects were due largely to the elevated and restricted movements of the diaphragm.

While the present study suggests that abdominal compression may be of value in the treatment of pulmonary diseases, there are no conclusions that it exerts a specific influence on the pulmonary lesions. The effects are regarded essentially as symptomatic responses. Apart from the value in treatment the supports may be useful in "testing" the effects of diaphragm elevation preliminary to proposed phrenicectomy, as was suggested in a personal communication from Dr. Henry A. Christian.

Conclusions. 1. The mechanism of diaphragm elevation has been studied with special reference to the occurrence of pulmonary symptoms in tuberculosis, bronchiectasis and emphysema associated with pneumoconiosis, chronic bronchitis and bronchial asthma.

2. The data suggest that a close relationship exists between the exaggeration of manifestations and the diaphragm operating at low levels with deep and uncontrolled excursions.

3. It seems possible that certain unfavorable results observed in the standard treatment of pulmonary diseases are due to inefficient diaphragm action. This may explain the occurrence of certain untoward effects attributed previously to the natural events of disease or to some special procedure.

4. It has been observed in certain patients that elevating and limiting diaphragm excursions by means of special abdominal supports facilitates expectoration, decreases cough and dyspnea, and influences most favorably the general condition.

5. The use of special abdominal supports is recommended as a supplementary measure in the management of pulmonary diseases.

Thanks are given to Dr. Leslie P. Anderson for assistance in the Roentgen ray studies, to Mr. Robert J. Titherington for assistance in making the silhouettes, and to Mrs. Millicent H. Maull for helpful coöperation in many ways.

REFERENCES.

1. Gordon, B.: The Effects of Abdominal Tumors on the Level of the Diaphragm, Proc. Interurban Club, Philadelphia, March 24, 1933.

2. Gordon, B.: Abdominal Conditions Influencing the Mediastinum and Pleural Pressure, Proc. Assn. Am. Phys., Washington, D. C., May 11, 1933; Am. Rev. Tuberc.

3. Alexander, H. L., and Kountz, W. B.: Symptomatic Relief of Advanced Emphysema, Proc. Assn. Am. Phys., Washington, D. C., May 11, 1933.

4. McCrae, T.: Osler's Principles and Practice of Medicine, 11th ed., New York, D. Appleton & Co., 1930.

THE TREATMENT OF TETANUS IN THE HOSPITALS OF LANCASTER, PA., OVER A PERIOD OF 30 YEARS.

By Anna P. Klemmer, M.D.,
JUNIOR PHYSICIAN, MEDICAL STAFF, LANCASTER GENERAL HOSPITAL,
AND
Edward S. Crosland, M.D.,
VISITING SURGEON, ST. JOSEPH'S HOSPITAL,
LANCASTER, PA.

Tetanus as a clinical entity has been recognized by the medical profession at least since the time of Hippocrates (460 to 375 B.C.) who mentioned the fatality of "spasm supervening upon a wound." Since the discovery of the tetanus bacillus and the production of a prophylactic serum great progress has been made in the prevention of the disease. However, much remains to be accomplished in the matter of successful treatment of established cases.

The purpose of this paper is to present a survey of the results obtained by various methods of treatment in Lancaster County over a period of 30 years. We have examined the records of this

disease in the two hospitals of Lancaster since 1903. In the first decade 1903 to 1913, there were 12 cases, from 1913 to 1923, 33, and from 1923 to 1933, 51. Because of the well recognized and startling symptoms of the disease and the generally accepted use of serum in treatment we believe that the hospital cases we have reviewed includes the majority of the actual cases of the disease in the county for the last decade. During the first two decades serum was less regularly employed and patients with tetanus were not hospitalized as regularly as today.

Lancaster, in southern Pennsylvania, is in one of the regions where tetanus is most prevalent.[1] Practically all of Lancaster County is under cultivation, with truck farming as a major industry. The ground is heavily fertilized with manure, and much of the farming is done by hand. These are doubtless factors in the prevalence of the disease in this locality.

In the past 30 years we have record of 96 cases treated for tetanus in the Lancaster General Hospital and the St. Joseph's Hospital. Of the entire series of 96 cases there were 55 deaths (57 per cent). We have been unable to find statistics published in any other locality covering a similar period of time for comparison, but judging by combined reports from various regions over shorter periods of time, it would seem that the mortality in these two hospitals has been about the average or perhaps slightly below. In our group of 96 cases, of the 11 who received no antitoxin, 3 recovered (mortality of 72 per cent). Of the 85 who received antitoxin, 47 died (mortality of 56 per cent). To compare with these figures, Lanphear,[2] of St. Louis, reported in 1899 that the cases treated without serum had a mortality rate of 80 per cent, and Bloom,[3] of New Orleans, stated that the mortality rate antedating the full use of serum was 85 per cent. The small number of cases we have on record treated without antitoxin does not give a sufficient basis for definite conclusions, but it gives us some slight idea of how the results obtained in Lancaster compare with those in other localities.

In our series, statistics based upon the amount of antitoxin given in each case seem to be useless because usually the size of individual doses was about the same, but in very severe cases the patient died after receiving only 1 or 2 doses, making the total amount of antitoxin very low. If the patient lived, the antitoxin was invariably continued over a long period of time and the total amount administered was, therefore, very high. The total amount of antitoxin per individual case in this series ranged between 5000 and 500,000 units (average, 71,000). In order to give some idea of results obtained by the administration of varying amounts of antitoxin we have calculated the amount of antitoxin given during the first day of hospitalization in each case. The amount of antitoxin given in the first few hours did not seem to depend so much upon the severity of the patient's symptoms, as upon the dose customarily ordered

by the attending physician. The amount most frequently given the first day was 10,000 to 20,000 units. The mortality statistics arranged in accordance with the varying doses of antitoxin for the first 24 hours is shown in Table 1. Up to 40,000 units there seems to be a very definite decrease in mortality with increase in initial dose; beyond this point, the reverse is true. However, since only a few cases received these very large doses, accurate deductions are impossible. It is difficult to gauge the severity of each case

TABLE 1.—MORTALITY AND AMOUNT OF ANTITOXIN USED.

Units of antitoxin administered in the first twenty-four hours.	No. of cases.	Died.	Mortality, per cent.
5,000 or less	13	8	61
10,000	14	9	64
12,000 to 15,000	10	6	60
16,000 to 20,000	22	10	46
25,000 to 30,000	6	2	33
40,000	8	2	25
50,000	4	3	75
50,000 to 100,000	8	7	88
Total cases receiving antitoxin	85	47	55
Total cases receiving no antitoxin	11	8	72
Total cases reported	96	55	58

from the intern's history, and it is questionable whether or not these large doses were given because of unusually severe symptoms. It is also difficult to ascertain whether death resulted from the acuteness of the disease or whether the amount of antitoxin given may have had some influence upon the outcome.

The results obtained by various methods of administration are shown in Table 2. The high mortality of the 9 intravenous cases (88 per cent) is, of course, based on a very small group for statistical

TABLE 2.—MORTALITY AND ROUTE USED FOR ANTITOXIN.

Route of administration of antitoxin.	No. of cases.	Died.	Mortality, per cent.
Intramuscularly	43	24	56
Intravenously	9	8	88
Intramuscularly and intravenously	14	2	15
Intraspinally, combined with any other method	19	13	68
Total cases receiving antitoxin	85	47	55
Total cases receiving no antitoxin	11	8	72
Total cases reported	96	55	58

value. The low mortality of the 14 cases who received mixed intramuscular and intravenous serum (15 per cent) should be noted. In examining the charts of the 19 cases receiving intraspinal combined with other forms of treatment, they do not impress one as having had more severe symptoms than the others, while the mortality rate (68 per cent) compares very unfavorably with the total

mortality rate of those receiving antitoxin (55 per cent). Furthermore, of the 13 patients who died after intraspinal antitoxin, 5 succumbed within 6 hours following the intraspinal injection. We have record of only 1 of the 13 having died in convulsions as did the majority of the other patients who died of tetanus. This raises the question of the safety of administering tetanus antitoxin intraspinally. In several cases it was impossible to ascertain whether a volume of cerebrospinal fluid equivalent to the volume of antitoxin given was withdrawn before the antitoxin was administered, but in some instances the quantity of cerebrospinal fluid removed was definitely stated and was certainly sufficient to avoid danger of increased intracranial pressure. In a small group of 4 cases, antitoxin was injected around the wound of entrance and into the trunk of the nerve supplying the area. Of these 4 cases, 3 recovered.

The period of incubation is said to be a very important factor in prognosis. Of the 4 cases developing tetanus within 5 days after the occurrence of the wound of entrance, 25 per cent died. Of the 37 patients developing tetanus in 5 to 10 days after the injury, 68 per cent died. Of the 17 patients developing tetanus 10 to 15 days after the injury, 53 per cent died, and of the 5 patients who developed tetanus more than 15 days after the injury, 46 per cent died. Thus in our series the highest mortality was found in those patients who developed tetanus between the 5th and 10th days after injury. This corresponds with a similar statistical report published by Osler[1] in 1907.

We were unable to arrive at any conclusion as to the influence of prompt treatment on mortality. In most cases treatment by tetanus antitoxin was instituted very soon after the admission of the patient to the hospital, but it is impossible to obtain from the charts any accurate idea as to how many hours before admission the first symptoms of tetanus appeared.

As to the frequency of the occurrence of tetanus in various ages, our 96 cases are divided as follows: 37 cases occurred in the first decade, 25 in the second, 8 in the third, 6 in the fourth, 7 in the fifth, 9 in the sixth and 4 in the seventh. Probably the frequency of occurrence in the first two decades is explained by the use of cap guns and fireworks, the habit of running about barefoot with open wounds of the feet, and the fact that smallpox vaccinations are made within this period.

A glance at the commonest wounds of entrance of the bacillus is enlightening (Table 3). Of the 10 that followed vaccination (10.4 per cent) with 6 deaths, we believe that the cases were due not to contaminated vaccine, but to soiling of partially healed vaccination wounds. The basis of this belief is the length of time elapsing between vaccination and the appearance of symptoms. In 2 cases we have no record of the date of vaccination. In 1 case a period of 10 days elapsed between vaccination and the appearance

of symptoms. In 6 cases the symptoms appeared 3 weeks after vaccination, and in 1 case, 1 month after vaccination. In several instances there is a statement on the history chart that the child was playing outdoors and injured the vaccination wound. A sterile dressing for the developed vaccine "take," similar to that applied to any other open wound, we believe should materially lower the incidence of tetanus. A tetanus toxoid is in the process of preparation at the present time which may prove of value when used in conjunction with vaccination. The commonest wound of entrance was the "splinter" wound (13 instances). The probable reason for the frequency of tetanus occurring in these cases is that the wound is ignored because it is so slight. Furthermore, a splinter wound provides the ideal anaërobic conditions for the growth of the tetanus bacillus. Of the 2 postpartum cases both patients died. One fatal case occurred following the injection treatment for hemorrhoids. In spite of the fact that other investigators have reported many cases following head injuries, in our series there were only 3 such cases. In 8 cases, no history of antecedent injury was obtained.

TABLE 3.—MORTALITY AND WOUND OF ENTRANCE.

Wound of entrance.	No. of cases.	Died	Mortality, per cent.
Lacerations	21	12	57
Various kinds of abrasions	19	11	57
"Splinter"	13	7	54
Vaccination	10	6	60
Puncture wounds	9	5	55
Powder burns	4	3	75
Other burns	1	1	100
Postpartum	2	2	100
Blisters on feet	1	1	50
Compound fractures	3	2	66
Injection of hemorrhoids	1	1	100
Abscessed teeth	1	0	0
Injury to middle ear	1	0	0
"Sore throat"	1	0	0
No history of wound	8	4	50

Of the 96 cases, only 14 occurred within the city of Lancaster. The others occurred in rural districts or in small suburban towns.

At least 1 and probably more of this series of 96 cases received a prophylactic dose of antitoxin within 2 weeks of the onset of symptoms, but accurate information on this point could not be obtained.

Of this entire group of cases 4 might be classed as mild cases, showing only rigidity of the jaw, irritability, etc., but no convulsions. The remaining cases could all be classed as severe, and the occurrence of severe convulsions was noted on 69 of the case records.

Summary. Data compiled from the records of 96 consecutive tetanus cases treated in the two hospitals of Lancaster over a period of 30 years is presented.

In our series, the patients who received intraspinal serum in conjunction with any other route of administration showed a mortality of 68 per cent, although the total mortality for all cases including the 11 who received no antitoxin, was only 58 per cent. The patients treated with intraspinal serum apparently had no more severe initial symptoms than those not so treated and we, therefore, believe that intraspinal tetanus antitoxin administration affords very questionable safety. It is interesting to note that in the small series of 14 cases who received mixed intramuscular and intravenous serum the mortality was only 15 per cent.

We were surprised to find that tetanus as a sequel to vaccination comprised 10.4 per cent of the total number of our cases. We believe that these cases were not due to contaminated vaccine but rather to improper care of the wound after vaccination. The most common wound of entrance was the "splinter," which caused 13 per cent of our cases.

The highest mortality was found in those cases who developed symptoms between the 5th and 10th day after injury.

Although one cannot draw definite conclusions from a small group, our series seems to indicate that the ideal dose of antitoxin in the first 24 hours is between 25,000 and 40,000 units. At least, doses less than 20,000 units in the first 24 hours would seem inadequate.

REFERENCES.

1. Osler, W.: System of Modern Medicine, Philadelphia, Lea & Febiger, **3**, 76, 1907.

2. Lanphear, E.: The New Treatment of Tetanus, Am. J. Surg. and Gynec., **13**, 4, 1899.

3. Bloom, J. D.: Tetanus Statistics, New Orleans Med. and Surg. J., **58**, 441, 1905–1906.

A MODIFIED MERCURIC CHLORID REACTION (TAKATA-ARA) IN CIRRHOSIS AND IN NEOPLASMS OF THE LIVER.

By Martin P. Crane, M.D.,

INSTRUCTOR IN MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA; ASSISTANT VISITING PHYSICIAN TO THE MISERICORDIA HOSPITAL, PHILADELPHIA.

(From the Medizinische Universitätsklinik Leipzig. Director: Professor Dr. Morawitz.)

The problem of distinguishing, particularly in late stages, liver cirrhosis from neoplasm, and certain other liver disturbances is often a very difficult and confusing one. Any procedure which renders this distinction more clear is therefore worthy of interest. The Takata-Ara test for establishing the diagnosis of liver cirrhosis has not as yet been investigated and reported in the American literature. The few reports in the European publications indicate that the test is of a high degree of specificity in this disease. The relative

simplicity of the performance of this test, together with what appears from reports to be its value, prompted its investigation in this clinic.

The test considered was originally proposed by Takata[1] and later by Takata and Ara[2] in 1925 as a colloid reaction in chest fluid, which would be useful in distinguishing between lobar and lobular pneumonia. They believed that it is the decreased stability of the serum proteins of the colloid system which makes precipitation with the mercuric chlorid-fuchsin solution possible. This they believed to be due to increased globulin. Necole[3] also concludes that the precipitate is due to a globulin effect. He believes that its albumin fraction exerts a protective action which opposes precipitation. In 1929, Staub[4] suggested that this colloid reaction if applied to blood serum might aid in determining the presence of liver cirrhosis. He based his suggestion on the probable alteration of the serum protein values in this disturbance. Jezler[5] investigated a series of cases and was able to add considerable confirmatory evidence to this suggestion. His original work was carried further in subsequent observations[6] in which the serum albumin-globulin relationship was studied. On the basis of the various studies certain explanations of the mechanism of the reaction have been advanced, and these will be subsequently discussed in brief.

Material. Studies were made upon the following: liver cirrhosis, 21 cases; hemochromatosis, 1; leukemia, with atypical cirrhosis, 1; early liver cirrhosis, 4; neoplasm involving the liver (secondarily), 6; acute yellow atrophy, 2; infectious and catarrhal jaundice, 5; toxic jaundice (chrysarobin-arsphenamin), 2; cholecystitis and cholelithiasis, 7; congenital hemolytic icterus, 2; liver abscess, 1; and miscellaneous disorders, which are catalogued in the table, 25 cases. The results in the series studies are shown in the tables. No attempt has been made here to report on entirely normal individuals, as this has been completely investigated by Jezler[5] with entirely negative results, which will, therefore, serve as sufficient control for cases herewith presented.

Method. Reagents: 0.9% sodium chlorid solution; 10% sodium carbonate solution; 0.5% mercuric chlorid solution; 0.025% aqueous fuchsin solution.

Into each of a row of 8 small glass tubes (those used for determining blood hemolysis are quite suitable) is placed 1 cc. of 0.9% sodium chlorid solution. To the first tube is added 1 cc. of blood serum, ascitic or other fluid. From the mixed content of the first tube 1 cc. is transferred to the second, the tube shaken, then 1 cc. transferred from Tube 2 to Tube 3, and this procedure is continued throughout the series. In the 8th tube the 1 cc. removed is discarded. The dilution of the serum or other fluid then ranges from 1 to 2 in the first tube to 1 to 256 in the last. To each tube is then added 0.25 cc. of the sodium carbonate solution and 0.3 cc. of the freshly prepared Takata reagent, which consists of a mixture of equal parts of the mercuric chlorid and aqueous fuchsin solutions. Readings are made immediately, and at ½-hr. and 24-hr. intervals. They depend entirely on the precipitate in the tubes. The precipitate at the end of 24 hr. is almost invariably the most definite and constant, since precipitate which appears at earlier

readings frequently diminishes or disappears on standing. Clouding and color changes are without importance; the same is true of the blue granular precipitate that sometimes occurs in the tubes of highest dilution, *i. e.*, the 7th and 8th.

In view of the fact that we are concerned only with precipitation and that color changes play no part in our reading, we have found it possible to omit the fuchsin. A further slight modification is the use of 6 tubes, rather than 8; for as previously mentioned, the precipitate in the last 2 tubes is without significance, and often occurs in distilled water alone.

The readings are made as minus (no precipitate); 1+, 2+, or 3+. Charting is of convenience, as shown in Fig. 1. After moderate practice, charting is unnecessary and readings are negative, positive, or, for the sake of comparison in cases that are followed progressively, strongly positive.

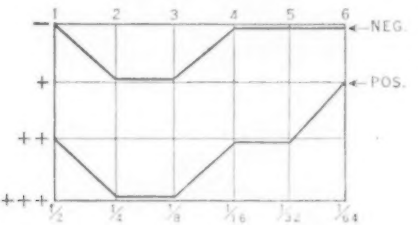

FIG. 1.—Typical negative and positive precipitation curves.

The standard by which positive reactions are judged is the appearance of a definite precipitate in 2 of the first 3 tubes, and at the same time a precipitate in any number of the following tubes, with the exceptions as previously noted. Positive reactions are usually quite characteristic, and negatives may have no precipitate in any tube, or a 1+ or a 2+ in any of the tubes from 4 to 7 alone. Figure 1 illustrates a typical negative, and a positive reaction curve. The latter curve may vary in form, but the variations are usually well on the positive side.

Blood if freshly collected must be centrifuged; due care must be exercised to prevent hemolysis, as it is possible that this may cause false positives. The presence of bile is without influence. Blood or other fluids may be preserved almost indefinitely on ice or with toluol. Ascitic fluid that contains blood or pus must also be centrifuged.

Results. *Cirrhosis.* The results obtained in this investigation agree very well with those of Jezler (Table 1). In the first group of 21 cases of advanced portal cirrhosis (Laennec) there were 20 positive reactions in both serum and ascitic fluid. The 1 negative case in this group was not seen in the clinic, the blood being examined only once. The diagnosis of cirrhosis had, however, been made upon good clinical grounds, and for this reason the case was included. In 1 case of hemachromatosis the reaction was strongly positive. The patient with myeloid leukemia has been reported more completely elsewhere;[7] he presented at autopsy a definite myeloid infiltration of the liver with an atypical cirrhosis, as well as what appeared to be old intrahepatic portal thrombosis. In the positive cases followed progressively to exitus the reaction did not in any case tend to diminish in degree of intensity, but as the terminal

stage of the disease appeared, the intensity of the reaction as judged by the amount of precipitate tended rather to increase. Esophagoscopy was performed on all but 1 of these cases with the Henning modification of the Wolff esophagoscope, to determine the presence or absence of esophageal varices, and gave positive findings in each instance. In 4 of the cases not coming to autopsy, laparoscopy was done by means of Henning's laparoscope through a small abdominal incision, to visualize the liver as an additional diagnostic measure. In the 4 cases described as "early liver cirrhosis," the patients all had fairly long histories of alcoholic overindulgence; livers were moderately enlarged and rather firm; all showed an increased urobilinuria. Three of the patients had gastric anacidity, and 2 had a moderate erythremia, with red blood counts ranging between 6 and 6½ million. None had ascites. The reaction was negative in all, and would therefore appear to be without value in these early cases.

TABLE 1.—RESULTS IN PORTAL CIRRHOSIS AND ALLIED CONDITIONS.

	No. cases.	Bichlorid test positive.		Esophageal varices.	Autopsy.	Operation.	Laparoscopy.	Other diagnoses.
		Serum.	Ascitic fluid.					
Advanced portal cirrhosis	21	20	20	20	11	2	4	Lues (6) Diabetes (2)
Hemochromatosis with cirrhosis	1	1	1	..	1			
Leukemia with atypical cirrhosis	1	0	0	0	1			
Early portal cirrhosis	4	0	0	0	0			

Liver Neoplasms. The reaction was negative in all 6 cases (Table 2). All were cases of secondary liver tumor, the primary growth being gastric carcinoma in 3, peritoneal carcinoma in 1, lung carcinoma in 1, and an abdominal sarcoma in 1. Five of the 6 patients had very marked hepatic enlargement and 3 had marked ascites. It would appear that in this type of case the reaction is of particular value in clarifying the diagnosis.

Other Liver Conditions. Of chief importance were 2 cases of acute yellow atrophy. The first, man aged 58, was deeply jaundiced and obviously quite ill for a period of 2 months, during which time he lost much weight. The reaction was positive during the course of his illness, but he improved spontaneously, and rapidly regained weight and strength. His jaundice disappeared, and the reaction was negative on discharge. The second case, a man aged 45, was deeply jaundiced over a period of 7 weeks, and died in coma. Diag-

nosis at autopsy was "acute yellow atrophy." The mercuric chlorid test was positive on all 4 estimations made during his stay in the hospital. We felt that the condition of these 2 patients was essentially the same, and that the reaction would seem to be of value in distinguishing this condition from simple catarrhal jaundice.

TABLE 2.—RESULTS IN NEOPLASMS, ACUTE AND CHRONIC LIVER DISTURBANCES AND CONTROL CASES.

	No. cases.	Bichlorid test positive.	
		Serum.	Ascitic fluid.
Neoplasms	6	0	0
Acute yellow atrophy	2	2 (1–)	0
Jaundice	18	0	
Other disease cases used as controls	26	0	
Infectious		1	
Catarrhal		5	
Toxic		2	
Abscess		1	
Cholecystitis cholelithiasis		7	
Congenital hemolytic icterus		2	
C. N. S. lues		1	
C. V. lues		1	
Nephritis		4	
Arteriosclerosis		3	
Thyrotoxicosis		1	
Polyserositis		1	
Lobar pneumonia		2	
Acute pulmonary tuberculosis		10	
Hypertensive heart disease		3	

The 18 cases with jaundice as the outstanding symptom were of significance in that they include a number of conditions that might be thought to render the reaction positive. Jaundice in these cases varied in duration from 1 to 10 weeks, and in intensity from moderate to very marked. There was some degree of hepatic enlargement in the majority of these patients, though this was transitory. Both in this group and in the others it was observed that the galactose tolerance test often bore no relation to the Takata-Ara reaction, the former quite frequently indicating hepatic functional impairment, while the latter was entirely negative. On the other hand, in cases of advanced cirrhosis with strongly positive Takata-Ara reactions, the galactose tolerance was normal. One case was examined in an acute hemolytic crisis, at which time the blood serum was quite red. Despite this, however, the reaction was consistently negative.

Non-hepatic Diseases. The final group represents a variety of pathologic conditions, which were examined chiefly as a means of control. Jezler[5] reports cases of nephritis, in which positive reactions were obtained; our cases were negative. Pongor[8] reports as high as 90% of positive reactions in patients with active pulmonary tuberculosis. In our 10 cases of active pulmonary tuberculosis in various stages of the disease, the reaction was entirely negative.

Discussion. Our results suggest certain possible causes for the production of a positive reaction: (1) extensive liver damage with the release of liver proteins (acute yellow atrophy) into the circulation; (2) an inability on the part of the liver to alter proteins that are contained in the blood; (3) the fact that some blood fails to pass through the liver, but passes directly from the splanchnic to the general circulation by way of collateral venous anastomoses. Certain phases of this problem are now under investigation in this clinic. The purpose of the present work has been to examine further the clinical application of this test.

Conclusions. 1. The application of a mercuric chlorid test (Takata-Ara) as an aid in the diagnosis of liver cirrhosis has been studied.

2. The results obtained confirm those of previous investigators as to its value.

3. Certain slight modifications are suggested for its performance.

4. The test is positive only in advanced cirrhosis, and is therefore of little value from the standpoint of early diagnosis.

5. Its chief worth lies in its differential diagnostic value to distinguish between cirrhosis and various liver neoplasms and other advanced liver disturbances.

REFERENCES.

1. Takata: Trans. 6 Congr. Far East Assn. Trop. Med., Tokyo, **1**, 693–699, 1925; in abstract, p. 585.
2. Takata and Ara: Trans. 6 Congr. Far East Assn. Trop. Med., Tokyo, **1**, 667–671, 1925; in abstract, p. 609.
3. Necole, R.: Ztschr. f. klin. Med., **110**, 94, 1929.
4. Staub, H.: Schweiz. med. Wchnschr., **11**, 308, 1929.
5. Jezler, A.: Ibid., **11**, 52, 1930.
6. Jezler, A.: Ztschr. f. klin. Med., **114**, 739, 1930.
7. Brugsch, H.: Persistent Thrombocythemia and Leukemia after Splenectomy, Fol. Hæmatol., **49**, 454, 1933.
8. Pongor, F.: Beit. z. Klin. d. Tuberk., **87**, 758, 1931.

Addendum to article on The Effect of Leukocytic Cream Injections in the Treatment of the Neutropenias.

By Max M. Strumia, M.D., Sc.D.

Since the completion of the article recently published in this Journal (**187**, 527, 1934), 3 more cases of malignant neutropenia have been treated with leukocytic cream.

BOOK REVIEWS AND NOTICES.

THE RENAISSANCE OF MEDICINE IN ITALY. By ARTURO CASTIGLIONI, M.D., Professor of the History of Medicine at the University of Padua. The Hideyo Noguchi Lectures. Publications of the Institute of the History of Medicine, The Johns Hopkins University, 3d ser., vol. 1. Pp. 91, 1 illustration. Baltimore: The Johns Hopkins Press, 1934. Price, $1.50.

THE first of the Hideyo Noguchi Lectures and first volume of the third series of publications of The Johns Hopkins Institute of the History of Medicine presents an important topic in a worthy manner. Such scholarly but pleasantly written historical work is bound to help the reader to a truer understanding of Italy's medical greatness in the Renaissance. From Pietro d'Abano through Lionardo, to Berengario, Cesalpino, Colombo, Fracastoro and Galileo we get satisfyingly clear pictures of how these and lesser lights lived in relation to their times; but, as in his *Storia* and *Volto d'Ippocrate*, the author is at his best in picturing vividly yet systematically the currents of medical thought that tumbled so boisterously yet constructively through the Italy of the 14th to 17th centuries. A delightful introduction by Sigerist shows us how this busy sanitation officer of a navigation company can do constructive scholarly work in the study and description of medical history. E. K.

THE MODERN TREATMENT OF SYPHILIS. By JOSEPH EARLE MOORE, M.D., Associate in Medicine, The Johns Hopkins University; Physician-in-Charge, Syphilis Division of the Medical Clinic and Assistant Visiting Physician, The Johns Hopkins Hospital. Pp. 535; 41 illustrations, Springfield, Ill.: Charles C Thomas, 1933. Price, $5.00.

THIS book is a successful effort to make available, in concise form, the present knowledge concerning the most effective modern methods of treatment in all phases of syphilis. The author's conclusions are based on his experience with the Johns Hopkins material, aggregating some 18,000 cases, on an unsurpassed familiarity with syphilologic literature and on the findings of the Coöperative Clinical Group now being published in coöperation with the United States Public Health Service. These conclusions are presented in an extremely readable and direct manner, the text being supplemented by numerous tables and outlines, most of which are extraordinarily informative and to the point. While the author scrupulously indicates the many controversial aspects of syphilotherapy, he has not hesitated to express his preferences definitely, usually with the most cogent reasons. The book is personal in tone but avoids the didacticism and evidence of prejudice so commonly found in books on treatment.

The arrangement of the book falls roughly into three divisions—a consideration of the biology of syphilis and of the collateral factors affecting the patient and his family, chapters on the individual drugs used and chapters on the various phases of early and late syphilis. The decline of mercury treatment is emphasized by the devotion of only 9 pages to it. One is struck by the author's flat refusal to endorse the use of sodium thiosulphate in arsphenamin dermatitis. Much valuable and new material on the treatment of blood dyscrasias following arsphenamin administration is presented. The chapters on the treatment of early syphilis, of cardiovascular involvement, of syphilis of the eye, particularly optic atrophy, and of neurosyphilis would be worthy of monographic publication, and reflect the author's many truly original contributions in these fields.

Wherever possible, clearly outlined schemes or systems of treatment are

given, although the author recognizes the impossibility of routinization in many cases. The superiority of arsphenamine (606) in early syphilis is strongly emphasized. A representative bibliography is included with each chapter, the necessary inclusion of many of the papers of the author and his associates being an indication of the authoritative background from which the book springs. The index covers 50 pages and is extremely complete.

This presentation of a complex and controversial subject is clear and dispassionate terms is distinctly an achievement. The book will prove of value to specialist and practitioner alike and should do much toward more intelligent treatment of one of the most mistreated of all diseases.

D. P.

KREBS IM LICHTE BIOLOGISCHER UND VERGLEICHEND ANATOMISCHER FORSCHUNG. 1. Band: Ectodermkrebs. By MED. DR. JOS. LARTSCHNEIDER, Linz a. d. Donau. Pp. 192; 43 illustrations. Leipzig: Franz Deuticke, 1934. Price, Rm. 10.–

COMPARATIVE anatomic investigations lead the author to conclude that the human epidermis and the epithelial lining of the mouth, esophagus, stomach and upper part of duodenum are not of ectodermal genesis, but are the products of mesodermal elements (leukocytes, connective-tissue cells, phagocytes, etc.) forming a coating tissue (Mantelgewebe). He believes that regeneration of this tissue does not take place in the germinative basal layer as commonly assumed, but results from the immigration of nuclei of leukocytes, etc. Another of the many startling and unbelievable revelations characterizing this book refers to the incomprehensible fact that sometimes even minor appendiceal irritations produce quick perforation. This is attributed to the fact that the protostomal end of the gastrulic entodermal sac becomes later the appendix, in which the tendency to form an opening persists.

W. H.

ON PHASIC INTRODUCTORY AND RELEASE EFFECTS OF THE COCAINE GROUP ON VESSEL PREPARATIONS AND AN ATTEMPT AT A GENERAL APPRAISAL OF PHASE EFFECTS. By EDUARD RENTZ, Riga. Translated and Abstracted by LINN J. BOYD, M.D., F.A.C.P. Pp. 146; 14 illustrations, n. p., n. d. [New York, 1933.]

EXPERIMENTAL observations on the changing vasoconstriction and dilatation effects of certain anesthetics, barium and suprarenin, their discussion, and literature pertaining thereto, occupy 41 pages. The remaining 92 pages contain a discussion of the theoretical possibilities involved in phasic phenomena, which are defined (in the translation) as "all transient and under certain conditions, reversely directed effects in spite of unaltered continuation of the stimulus, produced through various interferences and regardless of whether they have been evoked by the poison, its washing out or otherwise." An enormous literature (656 titles are listed in the bibliography) is cited to indicate to the author's satisfaction that phasic phenomena are not due to simple recovery, to tolerance, to "potential poisoning effects" (*i. e.*, to concentration equilibrium between interior of cell and environmental solution) or to opposite effects of high and low concentrations of a drug (the so-called Arndt-Schulz rule). The conception of an "apparent increase in excitability," developed by Fröhlich and von Frey to account for similar phenomena in striated muscle, is not mentioned, although it appears to the Reviewer to furnish an adequate explanation with some experimental support. The author concludes that phasic phenomena are of the same general nature as the spontaneous rhythm displayed by all sorts of living matter, and are probably similarly caused by changes in state of protoplasmic colloids—a conception which

cannot, of course, be denied, but which means little because even in the case of indifferent narcotics, in spite of innumerable investigations and an enormous mass of valid evidence, the nature of the responsible change in protoplasmic colloids remains a matter of controversy. The author has too often selected fragments of evidence which suit his immediate argument and no attempt is made to evaluate the validity or relative importance of most of the evidence cited. The translation is literal, often awkward, occasionally imperfect. The Reviewer does not share the translator's opinion that this monograph is valuable or important. C. S.

MENTAL HYGIENE IN THE COMMUNITY. By CLARA BASSETT, Consultant in Psychiatric Social Work, Division on Community Clinics, The National Committee for Mental Hygiene, etc. Pp. 394; 1 illustration. New York: The Macmillan Company, 1934. Price, $3.50.

MUCH has been written on mental hygiene by authors in many fields, but much of the writing has been limited to material related to one field. Usually such writings have been too indefinite for general use or have been largely propaganda. At least no publication in book form has appeared heretofore which classified mental hygiene as regards certain professions.

In this volume, however, the relation of mental hygiene is taken up in the field of medicine, nursing, social service agencies, parental education, pre-school child, teacher training, church, industry and from other important angles. The author aims not to present a brief for mental hygiene but to aid individuals, committees and communities, by presenting a panoramic sketch of how practical mental hygiene may be of importance and value. She fulfills this purpose well. Many good authorities are quoted and the huge amount of material has obviously been organized from reliable sources. The book is very easy reading. The material is presented in a very thoroughgoing manner. There is much detail, and the occasional redundancy is explained when we consider the numerous sections discussed.

An unusual feature is the presentation of questions and suggestions at the end of each chapter largely related to the development of mental hygiene in the particular field with which the chapter deals. This book will make an excellent text and reference book for communities and for professional people in general. It is not technical and not propaganda. It is simply a careful account of what mental hygiene actually is and what bearing it has on the lives and development of human beings. L. S.

THE ANATOMY OF THE RHESUS MONKEY (MACACA MULATTA). By Various Contributors. Illustrated by BENJAMIN KOPEL. Edited by CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, and WILLIAM L. STRAUS, JR., Department of Anatomy, Johns Hopkins University. Pp. 383; 125 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $6.00.

THE increasing use of the rhesus monkey as a laboratory animal in recent years has emphasized the need for a handbook of the gross anatomy of this species. This has been met by the coöperative activities of 19 American anatomists in a manner so admirable that the book could well serve as a model for future projects of a similar character. In addition to a succinct but adequate account of the gross anatomy, there are useful chapters on the groups and names of macaques, and on growth and development, as well as an appendix giving the methods of housing and care of monkeys, based chiefly on the rich experience of Dr. Corner, of Rochester, and Dr. Hartman, of Baltimore. The illustrations, which are uniform, clear and excellent, are chiefly pen and ink drawings done by a single

artist, Mr. B. Kopel. The Basle anatomic nomenclature, the standard for human anatomy, has been used, rather than the terminology of comparative anatomy. The book is a real contribution and the editors and other authors deserve both praise and gratitude. It will be of great use to the growing number of zoölogists, anatomists, physiologists and other medical scientists who use the monkey as a laboratory animal. E. C.

NEW BOOKS.

Allergy in General Practice. By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Professor of Medicine in the Cook County Graduate School of Medicine; Attending Physician, Cook County Hospital, Chicago. Pp. 339; 23 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1934. Price, $4.50.

The Span of Life. As Influenced by the Heart, the Kidneys and the Blood Vessels. By FRANKLIN R. NUZUM, B.S., M.D., F.A.C.P., Medical Director, Santa Barbara Cottage Hospital. Pp. 108; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $2.00.

"This book describes briefly, and in a manner understandable to the lay public, the functions of the heart, the kidneys and the blood vessels. The important changes that may occur in the structure of these tissues are shown and the causes of these changes, in so far as they are known, are given. It suggests measures for their prevention, and, once they become established, it outlines the management of these changes."

Formes, Vie et Pensée. By J. BEAUVERIE, and others. Pp. 419; illustrated. Lyon: Librairie Lavandier, n.d. Price, 20 fr.

Das Wunder der Heilung durch eigenes Blut. By DR. LUDWIG STERNHEIM, Pp. 64. Bern: Hans Huber, 1933. Price, Sw. Fr. 3.50.

A highly enthusiastic brief for autotransfusion, with a few case abstracts and an alphabetically arranged list of disorders in which it is recommended.

The Harvey Lectures 1932–1933, Series 28. Delivered under the Auspices of The Harvey Society of New York. By various contributors. Edited by DR. EDGAR STILLMAN. Pp. 233; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, $4.00.

Bright's Disease. A Clinical Handbook for Practitioners and Senior Students. By J. NORMAN CRUICKSHANK, M.C., M.D., D.Sc., F.R.F.P.S. (GLAS.), M.R.C.P. (LOND.), Senior Assistant to the Muirhead Professor of Medicine, University of Glasgow; Assistant Physician, Glasgow Royal Infirmary; Visiting Physician, Southern General Hospital, Glasgow. Pp. 208. Baltimore: William Wood & Co., 1933. Price, $3.75.

Cancer and Its Allied Diseases. By WILLIAM F. KOCH, A.B., A.M., PH.D., M.D. Pp. 308; illustrated. Detroit: By the author, 1933. (Price not given.)

A statement by the head of the Koch Cancer Foundation of his own views on cancer formation and its treatment by the Koch Cancer Foundation.

Cold Spring Harbor Symposia on Quantitative Biology, Volume 1. Pp. 239; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1933. Price, $2.90.

International Clinics, Vol. 1, Forty-fourth Series, 1934. By various contributors. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 320; many illustrations, 1 in color. Philadelphia: J. B. Lippincott Company, 1934. (Price not given.)

A new feature inaugurated in this volume is a supplement of 2 clinical case studies from the Pittsburgh Diagnostic Clinic, offered in order "to afford practice in the formulation of a diagnosis. Accompanying postcards can be filled out with check requests for the procedures which you feel are definitely indicated." Two packets will be returned, one giving the information requested, the other a final report by the Clinic staff.

Early Science in Oxford. By R. T. GUNTHER, Vol. IX. *De Corde* by RICHARD LOWER, London, 1669. With Introduction and Translation by K. J. FRANKLIN. Pp. 220; illustrated. Oxford: For subscribers at University Press, 1932. Price, £1, 1s.

The Greek Herbal of Dioscorides. Illustrated by a Byzantine A.D. 512; Englished by JOHN GOODYER A.D. 1655; Edited and First Printed A.D. 1933 by ROBERT T. GUNTHER, M.A., HON. LL.D. Pp. 701; 396 illustrations. Oxford: For author at University Press, 1934. Price, £3, 3s.

The Surgical Clinics of North America. Volume 14, No. 1 (Philadelphia Number, February, 1934). Pp. 226; 62 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, Paper, $12; Cloth, $16.

Students Aids Series. *Aids to Qualitative Inorganic Analyses.* By R. G. AUSTIN, B.Sc. (LOND.), A.I.C., F.R.M.S., Associate of University College, Southampton Demonstrator, St. Thomas's Hospital Medical School; Lecturer on Chemistry at Wimbledon Technical College, S.W. With an Introduction by R. H. A. PLIMMER, D.Sc. (LOND.), Professor of Chemistry in the University of London at St. Thomas's Hospital Medical School. Pp. 204. Baltimore: William Wood & Co., 1933. Price, $1.50.

"This little book is an attempt to provide, in as small a compass as possible, a well-tried system for the analysis of simple inorganic substances."

Students Aids Series. *Aids to Pathological Technique.* By DAVID H. HALER, M.B., B.S. (HONS.), Lond., Pathologist, Infants Hospital, S.W. 1; Battersea General Hospital, S.W. 11, etc. Pp. 187; 18 illustrations. Baltimore: William Wood & Co., 1933. Price, $1.50.

"This book is an attempt to give the student and other laboratory workers some ideas as to methods which have been found to work best in actual practice."

Students Aids Series. *Aids to Neurology.* By E. A. BLAKE PRITCHARD, M.A., M.D. (CAMB.), M.R.C.P., Assistant Physician, Hospital for Epilepsy, Maida Vale; Assistant in Medical Unit, Neurological Department, University College Hospital, London. Pp. 376; 43 illustrations. Baltimore: William Wood & Co., 1934. Price, $2.00.

"An attempt has been made to give a summarized account of the clinical conditions which most commonly result from disease of the nervous system."

Students Aids Series. *Aids to Botany.* By H. J. BONHAM, B.Sc., Biology Master, Crypt School, Gloucester. Pp. 221; 47 illustrations. Baltimore: William Wood & Co., 1934. Price, $1.50.

"This book, uniform with other volumes in the Students' Aids Series, has been modelled on the syllabuses of examinations normally taken in the Sixth Form of (English) schools, or at the end of the first year at Universities and Colleges."

NEW EDITIONS.

Treatment in General Practice. By HARRY BECKMAN, M.D., Professor of Pharmacology at Marquette University School of Medicine, Milwaukee. Pp. 889. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, $10.00.

Students Aids Series. *Aids to Anatomy.* By C. H. FAGGE, M.B., M.S. (LOND.), F.R.C.S. Pp. 333. Ninth edition. Baltimore; William Wood & Co., 1933. Price, $2.00.

"This edition is couched in the new anatomical terms. A glossary of the most noticeable changes from the old terminology which was used in the eighth edition will be found on pp. 302–306."

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

THE TREATMENT OF ERYTHREMIA (POLYCYTHEMIA VERA).

ERYTHREMIA, since the clinical description by Osler[1] in 1903, has been considered a definite entity, but lack of understanding of its true etiology has made all treatment rather unsatisfactory. Two etiologic factors have been considered: (1) A malignancy of the erythrogenic tissue comparable to the disease of the lymphogenic or myelogenic tissue known as leukemia; (2) a disturbance in the hormonal control of the bone marrow.[2, 3] This latter hypothesis has received considerable attention recently, due to the newer knowledge of the nature of pernicious anemia, a disease which in many respects presents an antithetical clinical and hematologic picture.

All successful forms of therapy have been directed toward reducing the number of red blood cells in the circulation and thus to relieve the two outstanding features of the disease, namely, increased blood volume and increased blood viscosity. The correction of these factors has been very successful in temporarily relieving the various symptoms and prolonging the life of the patient. It is questionable, however, whether the fatal termination of the disease is altered by therapy.

The problem of reducing the polycythemia and subsequently decreasing the total blood volume and blood viscosity has been attacked by two methods. The first is to reduce the erythrocytes in the circulating blood; this has been done by venesection and, to a greater extent, by the use of hemolytic agents. The second has been to reduce the activity of the erythrogenic tissue in the marrow, which is always in a hyperplastic state in the disease. Difficulties have arisen here because of the inability to obtain agents which can be easily controlled. If the dosage is too great, the erythrogenic tissue may be too greatly depressed or the platelets and leukocytes reduced to a dangerous degree.

The most widely used form of therapy today is phenylhydrazin.

This drug was first suggested for use in erythremia in 1918 by Eppinger and Kloss.[4] Recognized as a protoplasmic poison, as evidenced by experimental use of the drug in animals, it has proven very useful in erythremia. A normal erythrocyte count can be maintained in patients by phenylhydrazin given in therapeutic doses, without producing clinical liver or kidney damage, although when given to rabbits in large doses, it produces definite toxic destruction of these organs. This has been admirably demonstrated by Bodansky and coworkers in their study of the action of phenylhydrazin hydrochlorid and acetylphenylhydrazin. The chief effect of phenylhydrazin is to destroy erythrocytes, but it is possible that it also depresses the bone marrow to some degree.

One of the objections to phenylhydrazin hydrochlorid has been its tendency to produce toxic symptoms, even when used in very minute amounts. The most common of these are gastro-intestinal upsets, manifested by nausea, diarrhea, flatus, anorexia and abdominal cramps. Some patients complain of increased weakness and a feeling of pressure about the neck with this medication. This difficulty has been somewhat overcome by the introduction of acetylphenylhydrazin which, according to recent reports by Stone[6] and others, is as effective as phenylhydrazin hydrochlorid but does not produce toxic symptoms as readily.

The dosage of phenylhydrazin varies with the individual case. The usual procedure is to give the patient rather large doses, either daily or every other day, until the desired response is obtained. This is then followed by a maintenance dose that will keep the blood count at a normal level. If phenylhydrazin is given rapidly, there is a hemolytic crisis with jaundice and a rapid fall in the erythrocyte count. Better results are perhaps obtained if the drug is given more slowly and the hemolytic crisis avoided. Many have observed the rise in leukocyte count at the onset of the decrease in erythrocytes, but its value is doubtful as an aid in regulating the administration of the drug. The initial course should always be stopped before the desired erythrocyte count is obtained, because the drug has a cumulative action and may produce a severe anemia. The amount of the drug necessary to produce a normal erythrocyte count will vary considerably in each individual. This can only be determined by frequent blood studies and slow administration. A satisfactory procedure is to give the patient from 0.1 to 0.3 gm. every other day until the erythrocyte count approaches normal, then to put the patient on a maintenance dose. For some patients this will be as low as 0.1 gm. every 10 days, while others will require from 0.1 to 0.6 gm. weekly. Phenylhydrazin hydrochlorid and acetylphenylhydrazin require about the same dosage.

The organism does not seem to acquire a tolerance to the drug, though we may have a temporary phase of apparent tolerance ascribed to the increased resistance of newly formed erythrocytes. This is the explanation of the so-called tolerance as given by Bodansky. This phase is only temporary and, when there is a sufficient number of the mature cells in the circulating blood, there will again be a beneficial result from the drug. It is certain that equal doses given while the animal is still anemic will cause increasingly less blood destruction.[7] Some patients gradually require decreasing amounts of the drug after a

period of treatment. In a series of 37 cases reported by Griffin,[8] a few patients, after several years' treatment, were able to dispense with the drug completely. This may be due to the depressing effect of the drug on the bone marrow.

Phenylhydrazin should not be used indiscriminately, for there are several apparent contraindications to its use. Many have noted the development of thrombosis during the course of treatment. In a disease where thrombosis is so frequent, even in the untreated case, it is difficult to evaluate the rôle of phenylhydrazin in the production of this complication. With the increased blood destruction and rise in platelets that accompany phenylhydrazin administration, the tendency to thrombosis is probably temporarily increased. Because of this factor, Griffin and Conner[9] have pointed out that advanced cases requiring treatment in bed should not be given phenylhydrazin. Older patients with arteriosclerosis should be treated very cautiously with very small doses. The same is true in patients who have already developed thrombotic lesions. Patients confined to the hospital during treatment should not be kept in bed but should be allowed up and perhaps given massage, in addition, to keep the circulation active.

Irradiation (Roentgen ray, radium) has been used very extensively in erythremia, in many cases with very excellent results. The early reports were not as favorable as the more recent ones, due perhaps to the improved methods. Most observers agree that the best results are obtained by the use of depressing doses of the Roentgen ray over the long bones and chest. Irradiation of the spleen has given poor results. If the spleen is exposed at all, it should not have sufficient irradiation to depress its normal functions. With the therapeutic response from the depression of the marrow and the return of the erythrocyte count to normal, the spleen usually decreases in size.

The use of irradiation offers some difficulties. The dosage is difficult to regulate and the amount of depression of the erythrogenic tissue is not easily controlled. If the depression is marked, the patient may go into an anemic phase. This may be and is often accompanied by a depression of the leukocytes and platelets. To prevent such a complication during the course of irradiation, the blood should be followed closely and exposures stopped before the blood has reached the desired level; then, if more treatment is required, it can be given very cautiously. After a satisfactory course of irradiation, many patients have a prolonged remission lasting years, while others receive only temporary relief, necessitating a repetition of the course after a few months. Some patients, after an initial success, do not respond to subsequent irradiation.

In those cases with leukemia or pseudoleukemia combined with erythremia, radiation seems the most rational form of treatment. This has been used alone or combined with phenylhydrazin. It is likewise of value in patients who cannot be observed closely over a long period of time. Such patients must be watched during the period of exposure but, in the long remissions that may follow, frequent blood counts are not as necessary as with phenylhydrazin therapy. Such prolonged remissions have been observed by Milani,[10] who believes that the Roentgen ray is the best form of therapy available.

Venesection will produce very satisfactory temporary relief. The

effect, however, is very transient and the procedure has to be repeated frequently because it stimulates the bone marrow. However, in certain cases it has been found very useful for immediate relief of symptoms. It is also a safe procedure that may be used when conditions contraindicate the other accepted forms of therapy.

Opinions as to the value of spleen extracts vary. Lichtwitz and Francke[11] reported 2 cases with rapid fall in the erythrocyte count with spleen extracts and clinical improvement of the patient. The hemoglobin fell very little and slowly or may even rise, but the erythrocyte count became normal in 2 to 3 weeks. With cessation of the treatment the erythrocyte count rose again. There was apparent danger in the indiscriminate use of the extract, because anemia could be produced and frequent observations were necessary. The reports on the use of spleen extracts in this country have not been so favorable, the majority of observers having noted very little effect on the erythrocyte count. This may be explained by the observation of Kähler[12] that only a selected group of patients respond to the spleen extracts. The limited knowledge of the function of the spleen in a normal adult makes the rationale of this type of treatment questionable, but it is perhaps one that deserves further investigation.*

Benzol has been used by many in the treatment of erythremia, but is being replaced by other forms of therapy. The drug definitely depresses the erythrogenic tissue of the marrow but apparently has a greater tendency to depress the myelogenic tissue.[13] With its use, a marked leukopenia may develop and even a true myelophthisis of the bone marrow. Minot[3] regards this drug as dangerous and of no value in the treatment of erythremia.

Arsenic has been used by several observers in erythremia without very striking results. More encouraging is the report given by Forkner[14] in his series of cases of erythremia treated with potassium arsenite (Fowler's solution). The results, although not as dramatic as the use of this drug in chronic myelogenous leukemia, are quite encouraging, in that it offers an agent which is relatively non-toxic, the dosage of which is easily controlled. The drug is administered by mouth and in the reported cases the fall in red blood cells began as early as 10 days after the initial administration in some cases, while in others the fall did not take place until after weeks of treatment. Fowler's solution is given by mouth, after meals, beginning with 3 to 4 minims 3 times a day and increasing daily in gradual amounts until the desired effect is produced or until a total of 17 to 20 minims 3 times a day is administered. Forkner recommends starting with 3 to 4 minims 3 times a day for 2 days, then increasing the daily dose by 3 minims; in 2 days the dosage is increased further at the same rate until the first sign of intoxication, anorexia, is noted. This usually takes place when the patient is receiving 24 minims daily. After this, the drug is increased very slowly by 1 minim daily; by this method the dosage can be increased to 12, 15 or 20 minims 3 times a day. Potassium arsenite, like phenylhydrazin, requires a maintenance dose after a normal erythrocyte count is once reached.

* Numerous reports on the erythrogenic action of splenic extract would argue against the logic of this form of treatment, though it is, of course, possible that extracts prepared in different ways might have opposite effects.—Editor.

The vascular changes found in erythremia account for the majority of the symptoms. Those due to vascular distention and increased viscosity *per se* are relieved when the erythrocyte count has been reduced to a normal level. Those due to changes in the vessels themselves, such as thrombosis or endarteritis and a resulting infarction, present a greater problem in making the patient more comfortable. Not infrequently, such an accident brings the patient to a physician. The nature of these symptoms depends upon the location of the lesion, usually cerebral, abdominal or in the extremities. The last is quite common and the pain associated with such lesions is of chief concern to the patient. Such lesions not infrequently persist after the erythrocyte count is normal and require special treatment. Jacobi[15] reported immediate relief of symptoms in a case with peripheral arterial disease by the administration of physiologic saline solution intravenously. When the intravenous therapy was begun, the patient was also irradiated but, with the continuation of irradiation, the pain returned when the administration of the saline was stopped. Bernheim,[16] in 3 cases of erythremia with high blood viscosity, obtained a marked decrease in viscosity and symptomatic relief for at least 24 hrs. by the injection of 250 cc. of 2% buffered solution of sodium citrate. Other forms of therapy consist essentially of restoring the circulation by the development of collateral circulation.

In an attempt to find a more satisfactory form of therapy in erythremia, many procedures have been used which have proven ineffectual. Splenectomy was used and abandoned as unwise and useless. Barach and McAlpin[17] had 2 patients breathe 50% oxygen for a period of 2 weeks, with no significant decrease in the polycythemia. Rothman[18] used a high-fat diet, because of the hemolytic action of fatty acids, without significant results.

Recent hypotheses as to the etiology of erythremia suggest an entirely different approach in therapy. Several investigators have compared the symptomatology, physical findings and course of erythremia with pernicious anemia. Patton and his coworkers[19] have noticed frequently high gastric hydrochloric acid content and increased plasma cholesterol in erythremia and achylia and decreased plasma cholesterol in pernicious anemia. Both diseases have unexplained remissions. Several instances have been reported of patients with polycythemia developing anemia. Platt[20] studied a patient who, after developing erythremia, gave 39 transfusions over a period of 4 years and then developed an anemia with a low color index and typical glossitis, with improvement on liver therapy. This patient later developed the typical picture of erythremia. Minot and Buckman,[21] Klumpp and Hertig,[22] and others have studied patients who developed definite leukemic or pseudoleukemic phases during the course of the erythremia. This association certainly suggests a similar etiology.

Castle[23, 24] has demonstrated in normal gastric juice a substance which causes normal maturation of erythrocytes in patients with pernicious anemia. It is probable that pernicious anemia is caused by an insufficient elaboration of this principle. Morris[25] has designated this substance "addisin" and suggests that in patients with erythremia there is an oversecretion of addisin. The relation of erythremia to pernicious anemia then would not be unlike the relation of hyperthyroid-

ism to hypothyroidism. A similar hormone theory has been suggested by the work of Tuchfeld.[26] Morris suggests that a diet low in purin over a long period of time might be effective, in view of the fact that the sources of the hemopoietic substance effective in pernicious anemia have a high purin content (liver, kidney, stomach, nucleic acid). In support of the hormone theory, he reports a patient with erythremia and gastric ulcer who had frequent stomach lavages over a period of 6 months, with steady decrease in the blood count from 10 to 5.3 millions. When the lavages were discontinued, the erythrocyte count gradually increased to 10.2 millions at the end of 5 months.

The spontaneous remissions, which have been observed in erythremia, make the evaluation of any therapy difficult. The possible future isolation of a hormone, which is responsible for the increased activity of the erythrogenic tissue, may lead to a more rational therapy.

J. M. B.

REFERENCES.

1. Osler, W.: Am. J. Med. Sci., **126**, 187, 1903.
2. Harrop, G. A., Jr.: Medicine, **7**, 291, 1928.
3. Minot, G. R.: Cecil's Textbook of Medicine, 2d ed., Philadelphia, W. B. Saunders Company, p. 1006.
4. Eppinger, H., and Kloss, K.: Therap. Monatsh., **32**, 322, 1918.
5. Bodansky, M., Marr, W., and Brindley, P.: Am. J. Clin. Path., **2**, 391, 1932.
6. Stone, C. T., Harris, T. H., and Bodansky, M.: J. Am. Med. Assn., **101**, 495, 1933.
7. Bratley, F. G., Burroughs, H. H., Hamilton, D. M., and Kern, C.: Am. J. Med. Sci., **182**, 597, 1931.
8. Griffin, H. Z., and Allen, E. V.: Ibid., **185**, 1, 1933.
9. Griffin, H. Z., and Conner, H. M.: J. Am. Med. Assn., **92**, 1505, 1929.
10. Milani, G.: Ibid., **93**, 1205, 1929.
11. Lichewitz, L., and Francke, W.: Klin. Wchnschr., **8**, 17, 1929.
12. Kähler, H.: Deutsch. Arch. f. klin. Med., **166**, 105, 1930.
13. Reznikoff, P., and Fullarton, R.: Folia hæmatol., **50**, 454, 1933.
14. Forkner, C. E., Scott, McN., and Wu, S. C.: Arch. Int. Med., **51**, 616, 1933.
15. Jacobi, H. G.: J. Am. Med. Assn., **96**, 1138, 1931.
16. Bernheim, A. R.: Personal communication.
17. Barach, A. L., and McAlpin, K. R.: Am. J. Med. Sci., **185**, 178, 1933.
18. Rothman, H., Stern, J., and Hoens, P.: Ztschr. f. klin. Med., **123**, 620, 1933 (abstr., J. Am. Med. Assn., **100**, 1731, 1933).
19. Patton, W. D., Allardyce, J., and McKeown, T.: Canadian Med. J., **27**, 502, 1932.
20. Platt, R.: Brit. Med. J., **1**, 750, 1932.
21. Minot, G. R., and Buckman, T. E.: Am. J. Med. Sci., **166**, 469, 1923.
22. Klumpp, T. G., and Hertig, A. T.: Ibid., **183**, 201, 1932.
23. Castle, W. B.: Ibid., **178**, 748, 1929.
24. Castle, W. B., and Townsend, W. C.: Ibid., p. 764.
25. Morris, R.: J. Am. Med. Assn., **101**, 200, 1933.
26. Tuchfeld, F.: Med. Klin., **27**, 130, 1931.

THE PHARMACOLOGIC PROPERTIES AND THERAPEUTIC APPLICATIONS OF ALPHA-DINITROPHENOL (1-2-4).

Alpha-dinitrophenol (1-2-4) possesses striking pharmacologic properties. Recent observations have also revealed its therapeutic usefulness. The first systematic investigation of its biologic effects was conducted during the World War, as a result of observations of poisoning in munitions workers.[1, 2, 3] A more recent interest in the pharmacology of this substance has been revived by the systematic studies of

the fever-producing properties of nitrated naphthols by C. Heymans and his associates.[4, 5] Magne, Mayer and Plantefol,[6] Guerbet[7] and Tainter and Cutting and their associates[8, 9, 10] have undertaken a systematic study of the pharmacologic behavior of dinitrophenol. It was Tainter and Cutting, also, who first proposed its use in the treatment of obesity and in other conditions associated with lowered metabolism of the body.[11, 12]

Toxicologic Observations During the World War. The experiences gained during the World War, well described by Perkins,[3] have a particularly important bearing on the recently observed untoward therapeutic effects of dinitrophenol. The toxic effects of the explosives manufactured in Europe and the United States caused numerous fatalities among the workmen handling them. As far as dinitrophenol is concerned, it was thought at first that the toxic effect was due to some contamination. Soon it was found, however, that dinitrophenol itself, in the form of dust or vapor, may gain entry into the human body through the skin, the gastro-intestinal canal or the respiratory tract—the relative importance of these routes differing in various occupations. The skin was thought to be the most important portal of entrance in industrial poisoning.

Subacute intoxication usually manifested itself in anorexia with furred tongue, nausea, vomiting, diarrhea and colic. Rarely icterus was observed, due to the coloring properties of dinitropheñol, rather than to increased bile pigments. The workers often complained of weakness, loss of weight, headaches, and sweating. In *acute intoxication* the onset was sudden, usually with a sensation of intense fatigue, as if the circulation to arm and legs were "cut off." There was severe thirst, painful sensation of constriction at the base of the chest, agitation anxiety, dyspnea, elevation of the heart rate and fever. The urine was greatly decreased. In some instances of fulminating intoxication, death occurred within a few hours with general excitement and convulsions, followed by coma with unusually high temperature. Such a collapse developed at times while workers were walking home after a day of work without complaint. It was also noted early that in the fatal cases rigor of the body developed within 10 to 20 min. after death. A careful investigation by French and American observers soon established the fact that individual susceptibility played an important rôle in dinitrophenol intoxication, as only a limited number of workers developed intoxication under apparently identical conditions. Alcoholism, as well as the presence of albuminuria, has apparently predisposed to intoxication. There appeared to exist a relative susceptibility to dinitrophenol intoxication among white and a resistance among black workers.

Chemical studies have revealed that dinitrophenol changes partially or completely into its reduction products in the blood, tissues and urine. Among the reduction products found are: amino-2-nitro-4-phenol, amino-4-nitro-2-phenol, di-amino-phenol, and nitrogen compounds resulting from the combination of two molecules of amino-nitro-phenol, or of di-amino-phenol. Of these compounds the presence of amino-2-nitro-4-phenol indicates the presence of intoxication, and the demonstration of this compound in the urine is the basis of the violet reaction of Devrien.

Perkins[3] has also conducted *experiments* on horses, dogs, rabbits,

pigeons, turtles and frogs and has found that 0.01 gm. per kg. of body weight was toxic. All animals exhibited an exaggeration of their heat-radiation activities. He has pointed out that the fundamental phenomenon in all species of animals has been an extensive increase in the combustion of oxygen which is neither directly nor indirectly the result of stimulation of the nervous system. In experiments with *chronic intoxication* variable susceptibility was observed. All the animals lost weight. Perkins claims to have induced a tolerance in animals after repeated injection of non-fatal doses.

Recent Pharmacologic Contributions. As the experimental results of Belgian, French and American investigators[4–10] coincide in all the important aspects of the problem, they can be summarized as follows: Dinitrophenol is a yellowish-brown crystallin solid, only slightly soluble in water, or in physiologic saline solution. It can be dissolved up to 2% in ethylene or in propylene glycol. After the addition of about one-half its weight of bicarbonate of soda, it becomes soluble up to 3% in water. Such a solution of the sodium salt of dinitrophenol has a reaction of about pH 8.1 and is stable for years. The solution stains the skin and tissues. After its absorption it may produce a yellow color of the blood serum and of the sclera. The yellow color of the serum can be differentiated from the color of the bile pigment by the addition of 1 drop of 5% solution of hydrochloric acid, which absorbs the color of dinitrophenol, but not that of bile pigments.

Moderate doses affect all the species of animals tested in the same way. The first effect noted is an increase in respiration and in metabolism, present before there is any rise in temperature. In mammals, 5 mg. per kg. is the minimal and 20 to 30 mg. the maximal dose that induces fever. If higher doses are given, death may ensue before the temperature has reached its height (Tainter and Cutting[8]). The maximal febrile reaction after a moderate non-fatal dose occurs about 1 hr. after the subcutaneous or intramuscular injection. The fever may develop independently of the central nervous system and of the contraction of the stretched muscles, and is not prevented by ergotamin or by adrenalectomy and thyroidectomy.[9] If non-fatal doses are given, the effects subside usually 4 to 5 hrs. after the injection. Death in experimental animals may result from (*a*) direct circulatory depression, (*b*) hyperpyrexia, or (*c*) acidosis and anorexia.

Tainter and Cutting[9] have investigated the effect of repeated doses on the tolerance of the animal body to dinitrophenol. Administration of moderate doses at intervals of 3 or more days did not result in altered tolerance in 2 to 3 months. No evidence of toxic effects on the liver or other organs was found. The depression of the respiration induced by morphin, chloral, alcohol and barbital was counteracted by dinitrophenol. The efficacy of dinitrophenol was found to be comparable to that of caffein. The authors, however, pointed out that "the animals may still die, in spite of maintenance of adequate pulmonary ventilation." Dinitrophenol did not prevent death from just fatal doses of sodium barbital. It was found that the administration of physiologic salt solution and cooling by means of tepid baths exerted a partial antidotal effect.

Hall and others, in a subsequent study[10] investigating the effect of dinitrophenol on the metabolism and the circulation, found an elevation

of the oxygen consumption as early as 1 min. after the administration of dinitrophenol. After larger doses the oxygen consumption may amount to over tenfold the normal rate. The rise in the temperature is secondary to the increased oxygen combustion. There is a marked decrease in the liver and muscular glycogen, while the blood sugar and lactates tend to rise. The total carbohydrate disappearing has accounted for less than one-half the oxygen consumption; hence the principal fuel burnt must be other foodstuffs. The increased metabolism is maintained by increased minute volume output of the heart and by an increased arteriovenous oxygen difference.

Therapeutic Applications. The fact that animal experimentation has revealed that dinitrophenol, administered in relatively small doses, induces a considerable elevation of the basal metabolic rate without fever or other undesirable toxic manifestations, has suggested to Cutting, Mehrtens and Tainter its application in obesity and other conditions associated with low metabolism of the body. In their first clinical report,[11] they describe their observations on 8 patients to whom single doses of 3 to 6 mg. per kg. were administered orally. Following such doses the basal metabolic rate increased 20 to 30% in the first hour, and was maintained at this level for about 24 hrs. The normal basal metabolic rate returned on the third day. None of these subjects exhibited signs of nervousness, anxiety, trembling, hunger or palpitation. Following the administration of such daily doses for over 2 months, no changes in the heart rate or temperature were observed. When the dosage was raised to 5 or 10 mg. per kg., the temperature and the heart rate remained normal, but copious sweating developed. Doses above 10 mg. per kg. resulted in an elevation of the temperature of 3° C. The rate of respiration rose 15 to 30 per min. and the heart rate 20 to 30 per min. All the patients lost weight without restriction of diet. The greatest rate of loss of weight was 1.7 kg. per week. The average loss of weight, following a daily dose of 3 mg. per kg., was 0.9 kg. More vigorous doses combined with dietary régime have been purposely avoided. All the patients felt better following the administration of dinitrophenol. No hyperirritability was noted, and this is considered a distinct advantage over thyroid. The authors emphasize that they did not try the drug over a prolonged period, and hence they cannot express opinion on this point. They also urge against the administration of dinitrophenol in patients with diabetes.

In a subsequent report Tainter, Stockton and Cutting[12] describe more fully their experiences with 113 cases of obesity. These patients, mostly women, were not selected cases, and in about one-half of them dinitrophenol was administered only after thyroid and dietary régime had failed. The drug was administered in capsules containing 100 mg. of the sodium salt or its equivalent, 75 mg. of the acid. In this study the dosage was not proportional to the body weight, but it was given in accordance with the desired rate of weight reduction. The treatment usually started with the administration of 1 or 2 capsules with meals, and after the lapse of a week the medication was increased as necessary, until a weight loss of 0.9 to 1.4 kg. (2 to 3 pounds) was produced weekly. If the patient was on a special diet before the administration of dinitrophenol, this was continued; otherwise the patient maintained a normal diet. The average initial weight of the 113 patients was 85.5 kg.

(188⅜ pounds). The average length of treatment was 40 days, but some were treated as long as 125 days. The average loss of weight was 0.7 kg. (1½ pounds) per week. The average total loss was 4 kg. (8 4/5 pounds). The average dose was 2.9 capsules, corresponding to 1.5 capsules per 45 kg. (100 pounds) of the initial body weight. No general relationship existed statistically between a given dose and the resultant weight loss. While in 7 cases a dose of 1 capsule per day produced the normal loss of weight, in another group of 12 cases, 5 to 6 capsules had to be administered daily. The loss of weight takes place predominantly from the hips and abdomen.

True failure was encountered in 9 patients, in whom unpleasant side reactions such as cystitis, derangement of the taste, gastro-enteritis and skin lesions forced the discontinuance of the treatment. About one-fourth of the entire series of 113 patients complained of perspiration and sensation of warmth. The authors claim that the effect of dinitrophenol differs from that of thyroid. This is supported by the difference in the effects of dinitrophenol and of thyroid on the cholesterol metabolism and on tadpole metamorphosis.

Cutting and Tainter[13] have also reported on the metabolic action of dinitrophenol in man. The effect on the basal metabolic rate, on the nitrogen balance, on urinary organic acids, and on the body weight was studied in subjects on a balanced diet, and on an unbalanced diet with a maximal amount of carbohydrate, fat and protein. The drug was administered by mouth for 7 to 16 days. Although the basal metabolic rate rose from 30 to 50%, the subjects excreted less nitrogen than they ingested, and yet there was a definite loss of body weight. This indicates that the body proteins were probably not broken down. The output of the urinary organic acids was not increased, indicating that the fats were completely burned without giving rise to acidosis. The study indicates that under the effect of dinitrophenol carbohydrates and fats are primarily burned.

Masserman and Goldsmith[14] have studied the problem of whether the drug would be efficacious in increasing the subnormal metabolic rate often found in dull, depressed, listless and apathetic psychopathic patients. In this series the toxicity of the recommended doses seemed to be considerably higher than heretofore reported. The primary warning noxious action manifested itself in a fall of the blood pressure, onset of acidosis, progressive tachycardia and torpor. The evaluation of the psychotherapeutic activity was difficult, because of the possible spontaneous variations. Of 18 patients, 5 showed toxic reactions, in one instance resulting in death. Indeterminate or adverse psychotherapeutic effects were observed in 8 and 4 cases respectively. In 6 cases, improvement was attributed to the medication. The authors point out that dinitrophenol is unpredictably toxic to some patients. Anderson, Reed and Emerson[15] have reported a case with chronic hypertrophic arthritis, in which, after a total of 39.3 mg. per kg. over 14 days, severe intermittent joint pains appeared over areas previously not involved. This was considered as an allergic response to the drug. In discussing the toxicity of dinitrophenol, these authors remark: "In our opinion, it is yet to be demonstrated that this drug is as safe and satisfactory for weight reduction in human beings as other methods in common use." Geiger[16] reports the death from dinitrophenol of a physician

who took a very large dose, apparently with suicidal intent. Four hours after ingestion of the drug he became apprehensive, restless and uneasy. He felt warm and perspired freely. There was a sensation of air hunger, without dyspnea. The temperature rose to above 110° F., and following death there soon developed an intense rigor. It was estimated that the patient took a dose of 2.5 to 5 gm.—which is about 15 times the therapeutic dose.

While final judgment cannot be expressed as yet on the therapeutic value of dinitrophenol, the above analysis of the literature indicates that it is a substance which well deserves further trials in therapy. Its administration under medical supervision in doses advocated is apparently safe. Studies on its prolonged usage are still lacking.

S. W.

REFERENCES.

1. Barral, E., and Martin, E.: Lyon méd., **125**, 276, 1916.
2. Merklen, P., and Malloizel: Paris méd., **29**, 233, 1918.
3. Perkins, R. G.: Pub. Health Rep., **34**, 2335, 1919.
4. Heymans, C., and Bouckaert, J. J.: Compt. rend. Soc. de biol., **99**, 636, 1928.
5. Von Euler, U. S.: Arch. internat. de pharmacod., **43**, 67, 1932: **44**, 464.
6. Magne, H., Mayer, A., and Plantefol, L.: Ann. de physiol. et de physiochim. biol., **8**, 1, 51, 1932.
7. Guerbet, M.: Ibid., p. 92.
8. Tainter, M. L., and Cutting, W. C.: J. Pharmacol. and Exper. Therap., **48**, 410, 1933.
9. Tainter, M. L., and Cutting, W. C.: Ibid., **49**, 187.
10. Hall, V. E., Field, J., 2d., Sahyun, M., Cutting, W. C., and Tainter, M. L.: Am. J. Physiol., **106**, 432, 1933.
11. Cutting, W. C., Mehrtens, H. G., and Tainter, M. L.: J. Am. Med. Assn., **101**, 193, 1933.
12. Tainter, M. L., Stockton, A. B., and Cutting, W. C.: Ibid., p. 1472.
13. Cutting, W. C., and Tainter, M. L.: Ibid., p. 2099.
14. Masserman, J. H., and Goldsmith, H.: Ibid., **102**, 523, 1934.
15. Anderson, H. H., Reed, A. C., and Emerson, G. A.: Ibid., **101**, 1053, 1933.
16. Geiger, J. C.: Ibid., p. 1333.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

MALACIC DISEASES OF BONE.

PRESENT-DAY interest in this subject was focused in a symposium conducted at the annual meeting of the American Roentgen Ray Society in September, 1932.

Dresser[1] distinguished osteitis fibrosa cystica unassociated with an endocrine disturbance from that which is a manifestation of a systemic disease caused by overactivity of the parathyroid glands. He dealt

particularly with the latter, however. MacCallum[2] first showed that hypofunction of the parathyroid glands resulted in tetany, the symptoms of which could be relieved by administration of calcium. The fact that these glands exercise a control over calcium metabolism was thus established. Mandl[3] definitely established the relation of parathyroid dysfunction to osteitis fibrosa cystica by removal of a parathyroid adenoma.

Increase in the calcium content of the blood, lowering of the blood phosphorus, increased elimination of calcium and phosphorus by the kidneys, and decalcification of the bones result from overactivity of the parathyroid glands. The disease may occur at any age, in either sex, but it most commonly affects women between 30 and 60 years of age. Most patients complain, first, of pains in bones and joints. In the advanced stages, skeletal deformities may develop as the result of softening, bending, and fractures of the bones. Gastro-intestinal symptoms are not uncommon: loss of appetite, nausea and occasionally vomiting. There are usually slow, progressive loss of weight, and secondary anemia. There may be a palpable tumor in the neck (parathyroid adenoma). The urinary symptoms are important. Renal function is impaired. Polyuria is frequently present and the urine is of low specific gravity and contains albumin and casts. The increased output of calcium and phosphorus leads to the formation of urinary calculi, which may be bilateral. Any abnormal rarefaction of one or more bones of a patient who presents renal calculus should be regarded as ground for suspecting osteitis fibrosa cystica. A correct determination of the blood calcium and phosphorus is essential to the diagnosis. The concentration of serum calcium is elevated (more than 10 mg. per 100 cc.) and the serum inorganic phosphorus is low (less than 4 mg. per 100 cc.). The parathyroid tumors which have been described, vary in size from a few mm. to 5 or 6 cm. in diameter. The microscopic picture is that of an adenoma which may be difficult to distinguish from normal parathyroid tissue. Abnormal deposits of calcium in the soft tissues have been described. The roentgenologic findings are: (1) Generalized decalcification of bone together with localized regions of increased density of bone; (2) generalized or localized formation of cysts. Generalized osteoporosis may be seen without formation of cysts, and conversely, formation of cysts may occur without appreciable osteoporosis. The bones of the skull present mottling of the vault which is the result of small, irregular areas of condensation of bone alternating with areas of rarefaction. In advanced stages of the disease the cranial bones may become much thickened. The upper and lower jaws are both favorite sites for formation of cysts. The teeth are often carious and abscessed. There may be abnormal curvatures of the spinal column, which become more pronounced as the disease progresses. The vertebral bodies are narrowed, the bony texture is altered, and the articular surfaces have a tendency toward concavity. The intervertebral spaces are not narrowed and the vertebral processes do not appear abnormal. The pelvis is frequently the site of very extensive cystic changes, and abnormalities of contour develop as the weakened bones give way to the body weight. The ribs are fairly regularly involved in the cystic process, and late in the disease the thorax may cave in with serious cardiac and respiratory embarrassment.

Cysts occur in all the long bones and in the bones of the hands and feet. The bones may become expanded and the cysts trabeculated, producing the appearance of a giant-cell tumor, or there may be localized areas in which bone trabeculæ are completely lost, but without expansion or other alteration in the contour of the bone. Fractures of the extremities are common and seem to heal readily, but without excess of callus. A cyst which has been the site of spontaneous fracture or surgical interference often will regress rapidly. Too sharp a distinction should not be drawn between localized and generalized osteitis fibrosa cystica.

Ballin[4] stated that if a parathyroid gland were irritated by hyperplasia or by an adenoma, its function would be stimulated and, as a result, more parathormone would get into the circulation. This increased parathormone leads to decalcification of the skeleton, through increase in the calcium content of the blood serum; the calcium is derived from the great calcium storehouse, the skeleton. In addition to the train of symptoms described by Dresser, Ballin stated that hypercalcemia leads to lessening of the muscle tonus and to secondary deposits of calcium in certain places where infection or other conditions may cause roughening and thus make an especially inviting location. Microscopic examination also reveals widespread deposits of calcium in the liver, spleen, intestinal mucosa and kidneys. Ballin stressed these latter in the consideration of certain cases in which Oppel claimed arthritis resulted from parathyroidism. If hypercalcemia exists, secondary deposits of calcium will lead to ankylosis in cases of otherwise non-ankylosing arthritis and, therefore, parathyroidectomy will prevent and even cure some of these beginning cases. To diagnose them, evidences of other disturbances of parathyroid function, such as hypercalcemia or severe muscle hypotonia are necessary. Cases of parathyroidism without demonstrable involvement of bone have occurred. Absence of hypercalcemia and other chemical data should not invalidate the diagnosis of parathyroidism if clinical and Roentgen findings and hypotonia, for example, favor the diagnosis.

Morse,[5] continuing the survey of malacic diseases of bone, in a first group placed those diseases in which the primary defect is in the mesoblast. The mesoblastic tissue as a whole, all over the body, is probably defective and, as a result, the ability of the osteoblastic cells to lay down the connective-tissue groundwork for bone is lacking. The bones are fragile not because there is any primary defect in calcium metabolism, but because the connective tissues are unable to build up a groundwork on which enough lime may be deposited. In this class come osteogenesis imperfecta and fragilitas ossium, probably the same disease; the first the fetal or infantile manifestation, and the second an adult form. These diseases have a particular tendency to be hereditary and familial, to be characterized by multiple fractures which heal normally, to give evidence of their presence by the characteristic blue sclera of those affected, and also to show various evidences of multiglandular endocrine disturbances of more or less indefinite form. The blood calcium and phosphorus levels are usually normal. In the second group he placed those diseases which are due to a primary defect in absorption and fixation of lime; either the intake of calcium is deficient in general, or is insufficient to meet an unusual physiologic demand, or the intake of vitamin D is deficient or all of these factors combined

have an effect. Rickets and osteomalacia proper are in this class; rickets is the infantile, and osteomalacia the adult type of the same disease. Here there is no mesoblastic defect; there is no deficiency of connective tissue, and no lack of capacity on the part of the bone-forming cells to lay down sufficient groundwork for lime to be deposited on, but the dyscrasia is one having to do with the inability to fix lime in the new forming bone or with inability to obtain enough lime for this purpose. In these cases there is usually no elevation in the levels of blood calcium. The levels of phosphorus are also usually normal, except in those atypical forms of rickets known as high-phosphorus rickets which probably have other relationships. Secondary hyperplasia of the parathyroid gland is the rule, but ordinarily rickets and osteomalacia are not primarily parathyroid in origin and not ordinarily amenable to surgical treatment. In cases of a third group, the general characteristic is increased excretion of lime in the urine, a sort of leakage of lime, due possibly to various causes but associated with various diseases of other endocrine glands. The malacia involving bone in severe cases of exophthalmic goiter, that in pancreatic diabetes with marked sclerosis of the pancreas (possibly related to a chronic acidosis), the decalcification of bone in some cases of basophil adenoma of the pituitary body, and certain cases of suprarenal tumor, make up this group. Renal rickets presents a most striking form of malacia of bone; the primary defect probably is retention of phosphorus. The result of this retention of phosphorus is marked responsive hyperplasia of the parathyroid gland, undoubtedly brought about in an effort to lower the level of blood phosphorus; its secondary result is to increase the concentration of blood calcium, to draw on the reserve of lime in the skeleton, and diffusely to decalcify the bones. Removal of the parathyroid gland, or any other therapeutic measure undertaken with the idea of alleviating the affection is not to be considered. In a group that must be distinguished from others, Morse placed those diseases in which defects in bone are produced by pressure erosion: Hand-Schüller-Christian's disease, Gaucher's disease, Niemann-Pick's disease and Hodgkin's disease. The roentgenologist often finds it difficult to separate members of this group from various others which truly belong in the classification of malacia. Generalized carcinomatosis might also be placed in the same category. In a single group, as caused either by primary parathyroidism, or at least by overactivity of the parathyroid gland brought on by some special cause, Morse placed osteitis fibrosa, osteitis deformans (Paget's disease), leontiasis ossium, the ankylosing polyarthritis of Oppel, multiple and possibly single giant-cell tumor and multiple myeloma of the plasma-cell type. The evidence at present seems to him to point to the fact that operation and removal of some of the parathyroid glands lead, in most cases, either to complete clinical cure or at least to marked clinical benefit. He considered myeloma to be a primary osteoblastic tumor arising from the primitive osteoblasts and at present a malignant manifestation or a malignant end-stage of osteitis fibrosa cystica.

Bromer[6] regarded fetal rickets as a definitely established clinical entity. Infantile rickets may be seen in two types: the passive type is seen in severe cases, and the infant, because of muscular weakness, does not move the extremities; the active type affects children who are

of a good state of nutrition and bodily activity, in spite of the rickets. Bromer distinguished three stages seen roentgenographically, covering the progress of the disease from the first roentgenologic signs to complete healing.

Hodges and Ledoux[7] affirmed that osteomalacia is the rickets of adults and quoted McCrudden's careful work and his interpretation of microscopic and chemical studies as showing that the physiologic destruction of old bone and its replacement by new osteoid tissue went forward in a normal fashion, but that for some reason the calcium liberated from the old bone was not utilized by the organism to calcify the new osteoid tissue, but instead was lost from the body, principally in the feces. The treatment of osteomalacia is the treatment of rickets: a diet adequate in all respects, particularly in vitamin D, plus an adequate amount of sunshine.

Peirce[8] did not feel that evidence is sufficient at present to justify placing giant-cell tumor in the group of "primary parathyroid osteomalacias." Hall[9] suggested that the toxins from the same infectious process that plays a major part in the etiology of spondylitis act as parathyroid stimulants, so that parathyroidism becomes the most important, if not the primary, factor in producing the para-articular changes. As to whether there may not be a hereditary or familial tendency to parathyroid dysfunction to explain the quite generally accepted hereditary factor in spinal ankylosis of the Bechterew type is a problem worthy of careful study. Osteopoikilosis, according to Wilcox,[10] is characterized by a disseminated condensation of the bones of the skeleton, without clinical symptoms. All of the bones have been shown to be involved, except the bones of the skull. Three types have been described: the spotted form, which is the one most commonly seen; the striated form, which is relatively rare and in which there are long, narrow striations of dense bone, and the mixed form, which is a combination of the two. It is a hereditary anomaly developing from a congenital anlage. Neither osteopoikilosis nor marble bone, in the opinion of Pirie[11] offers any suggestion of being related to the parathyroid gland.

Vogt[12] pointed out that renal rickets is a term used to denote rachitic changes in bone sometimes associated with chronic nephritis in children. It is not a primary entity, but a manifestation of disturbed mineral metabolism resulting from renal disease. Rickets, as seen in infants, is a deficiency disease, that is, certain vital factors essential to anabolism of bone are lacking. Vitamin D acts as a regulator of calcium and phosphorus metabolism and permits the organism to operate with greatly increased economy with respect to these minerals. The concentration of calcium and inorganic phosphorus in the serum is determined by at least four factors; namely, the calcium content of the diet, its total phosphorus, the ratio of these components in the diet, and the amount of vitamin D preformed or produced by radiation. Without the balancing effect of vitamin D, calcium and phosphorus in the serum vary directly with concentration of the same elements in the diet. Furthermore, there seems to be antagonism between calcium and inorganic phosphorus. A high concentration of one element depresses the concentration of the other component in the serum. The primary factor responsible for the bony changes of rickets is an imbalance or deficiency

of calcium and phosphorus in the blood. The pathognomonic histologic lesion is due to defective mineralization of growing bone. Renal disease is recognized as one of the factors in alteration of the levels of the inorganic constituents of the blood. Therefore, in certain types of nephritis, conditions are present which are favorable for the development of rickets. Roentgenologic findings vary in different cases, and sometimes in the same case at different times. Skeletal development is always retarded, and disturbances of growth are often manifested by the presence of transverse striæ near the ends of long bones. The lesions may be asymmetrical, or different bones may be unequally involved. Roentgenograms of the skull show fine, granular mottling and generalized osteoporosis. There is irregular mottling of the anterior ends of the ribs and defective subperiosteal calcification along the lateral margins. The ends of the diaphyses are identical in appearance with that produced by ordinary rickets. Defective subperiosteal calcification is seen at the upper ends of the tibiæ, medially; the metaphyses are smooth and dense. Osteogenesis imperfecta is a deficiency of osteoblasts, resulting in deficient ossification of bone, this being productive of numerous and repeated fractures. On chemical analysis there is no lack of the inorganic constituents of bone, and fragility therefore cannot be dependent on this factor. Bromer[13] found but one reference to an actual pathologic finding in the parathyroid bodies in such a case. This was a case of bone dysplasia and unusual vascularity of the parathyroid glands, with a relatively small amount of parenchymal tissue. In an appended note he tabulated 3 other cases in which, histologically, there was hyperplasia of the parathyroid glands.

Golden and Abbott[14] concluded that hyperthyroidism produces an abnormal elimination of calcium, the mechanism of which is not understood. It seems to be frequently associated with decalcification of the bones demonstrable in the roentgenogram by suitable comparison with the normal; the decalcification is so slight as to be of little if any importance. In rare cases the decalcification of the bones may be extreme. Its appearance, however, is not characteristic of thyrotoxicosis. In cretinism and infantile myxedema there is widening of the cortex of the long bones, without loss of calcium. Hypothyroidism in adults apparently is associated with no greater incidence of decalcification of bones than that which might be encountered in any group of patients of the same age. Although suprarenal secretion either directly or indirectly influences calcium metabolism, and although the suprarenal glands may be indirectly involved in a pluriglandular imbalance in certain cases of osteomalacia, the evidence does not seem to justify the assumption that decalcification of the bones results directly from suprarenal disease or dysfunction. The available evidence indicates that loss of calcium may take place in diabetes, especially with acidosis. The question is how much of this is of endocrine and how much of nutritional origin. Roentgenologic evidence of definite important skeletal decalcification in diabetic adults is lacking.

Hand-Schüller-Christian's disease, according to Rowland,[15] is a rare, probably familial, constitutional disorder of metabolism in which a deposition of lipoid mixtures, particularly cholesterol and its ester, takes place, leading to a characteristic hyperplastic reaction in the reticular endothelial or the histiocytic apparatus. The common patho-

logic change is a granuloma-like accumulation arising from connective tissue in many parts of the body. Usually three cardinal symptoms, bony defects, exophthalmos and diabetes insipidus, are present but it should be understood that no one of these is essential and that there are others which are sometimes of equal importance. The resorption of bone resembles that of osteomalacia in many respects; that is, atrophy with demineralization, although it is really atrophy of bone from pressure. The membranous and flat bones are most often involved, but changes may occur in any part of the skeleton. Roentgenographically, changes in the superior and inferior maxillæ, flat bones of the pelvis, scapulæ, ribs, vertebræ and the long and short bones have been observed. When there has been involvement of the pituitary gland, destructive changes in the sella and Roentgen evidences of tumor have been noted. The endocrine disturbance seems to be the result of the lipoidosis.

Erythroblastic anemia (Cooley's syndrome) has been thoroughly reviewed by Baty and others.[16] Borzell[17] has compiled the characteristic roentgenographic findings as striations in the calvarium with trabeculation of the facial bones, clavicles, scapulæ, and long bones with expansion of the shaft and thinning of the cortex in the latter. The changes in sickle-cell anemia are similar in some respects to those found in erythroblastic anemia, but not by any means as profound. With any improvement under radiotherapy there appeared a greater tendency to transverse striation, particularly at the metaphyses, together with definitely increased density of the metaphyses. In the rapidly accumulating literature on this subject one finds criticism of some of the assertions made in the foregoing articles. Bauer[18] stressed the point that all cases thus far reported have been due to parathyroid adenoma. The serum calcium in these has been permanently elevated.

Nachlas[19] studied the serum calcium in 37 cases of arthritis and found no change from normal. In the same patients the blood phosphorus was studied with the idea of distinguishing hypertrophic from infectious arthritis, but no uniform variation from the normal reading was obtained. Compere[20] confirmed the opinion that the only definite test of parathyroid hyperfunction which is acceptable is the study of calcium metabolism and the demonstration of a negative calcium balance. The balance is consistently negative; the serum calcium is high; the plasma phosphates are low, and true adenomas of one or more of the parathyroid glands are found in nearly all cases at operation or postmortem examination.

A. M.
C. G. S.

REFERENCES.

1. Dresser, R.: Am. J. Roentgenol., **30**, 596, 1933.
2. MacCallum, W. B.: Quoted by Dresser.
3. Mandl, F.: Wien. klin. Wchnschr., **38**, 1343, 1925.
4. Ballin, M.: Am. J. Roentgenol., **30**, 571, 1933.
5. Morse, P. F.: Ibid., p. 578.
6. Bromer, R. S.: Ibid., p. 582.
7. Hodges, P. C., and Ledoux, A. C.: Ibid., p. 590.
8. Peirce, C. B.: Ibid., p. 604.
9. Hall, E. W.: Ibid., p. 608.
10. Wilcox, L. F.: Ibid., p. 615.
11. Pirie, A. H.: Ibid., p. 618.

12. Vogt, E. C.: Ibid., p. 624.
13. Bromer, R. S.: Ibid., p. 631.
14. Golden, R., and Abbott, H.: Ibid., p. 641.
15. Rowland, R. S.: Ibid., p. 649.
16. Baty, J. M., Blackfan, K. D., and Diamond, L. K.: Am. J. Dis. Child., **43**, 667, 1932.
17. Borzell, F. F.: Am. J. Roentgenol., **30**, 657, 1933.
18. Bauer, W.: J. Bone and Joint Surg., **15**, 120, 1933.
19. Nachlas, I. W.: Ibid., p. 151.
20. Compere, E. L.: Ibid., p. 142.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 19, 1934

The Effect of Removal of the Adrenal Glands Upon Pancreatic Diabetes in the Cat. C. N. H. Long and F. D. W. Lukens (George S. Cox Medical Research Institute, University of Pennsylvania). In the past numerous attempts have been made to show that the adrenals play some part in the chain of events that follows pancreatectomy, but the most authoritative workers have concluded that no such interrelationship exists. However, in recent years it has been abundantly demonstrated that hypophysectomy, either before or after removal of the pancreas, greatly ameliorates the subsequent course of the diabetes. The final pertinent fact that led us to attempt another investigation of the relation of the adrenals to pancreatic diabetes in certain animals is that hypophysectomy causes a marked atrophy of the adrenal cortex and might be producing its effects through these glands.

In 5 cats we have removed, in stages, all the pancreas and both adrenal glands. The periods of survival were 12, 11, 8 and 6 days, while another animal was sacrificed in good health on the 7th day for liver glycogen determination (2.5 gm. %). One of the animals was diabetic at the time the second adrenal was removed. Its subsequent behavior was no different from the others.

None of the animals presented the usual clinical picture of those depancreatized with the adrenals present. They remained active and ate fairly well up to the day of death. They have all died suddenly in convulsions in marked contrast to the ordinary diabetic cats, which gradually sink into coma. A commercial preparation of adrenal cortical extract was injected daily, but not insulin. Although supposedly adequate amounts of cortical hormone were given, the animals resembled in some respects those suffering from adrenal insufficiency.

The most striking findings have been (*a*) the fasting (overnight) blood sugars in the majority of observations were not above normal and showed a remarkable tendency after the first few days to fall to such low levels that convulsions, relieved by glucose, have supervened. (*b*) The daily glycosuria was very mild or absent, depending upon the

amount and type of diet. When glycosuria was present the $\frac{D}{N}$ ratios were not those of pancreatic diabetes. (*c*) Metabolic balance sheets reveal that large quantities of the glucose of the diet were utilized but the tolerance was not normal. (*d*) The feeding of glucose by stomach tube or its intraperitoneal injection gave variable results. The animals showed a practically normal tolerance at some times, while at others it was decreased.

In 7 animals similar experiments were carried out but one adrenal was left intact; 3 of these were not treated with insulin and died of a rapidly progressing and typical diabetes in 5 days or less. The remainder were treated with insulin. Three showed no diminution in their insulin requirement on a standard diet. The remaining animal had an increased sensitivity to insulin for the first week after the last of the pancreatic tissue was removed. Following this the usual amounts of insulin were required.

While this work was in progress there appeared a paper by BARNES, SCOTT, FERRILL and ROGOFF (*Proc. Soc. Exp. Biol. and Med.*, **51**, 524, 1934). These workers report that if unilateral adrenalectomy is performed on dogs prior to total pancreatectomy, the course of the ensuing diabetes is very mild. Furthermore, unilateral adrenalectomy, after total pancreatectomy either enables the animal to exist on greatly reduced amounts of insulin or to live for a long time without any.

At the present time we have 1 dog in which unilateral adrenalectomy was performed before total pancreatectomy. It appears to differ from the cats with these operations but it is too soon to draw any conclusions. The possibility of a species difference is considered.

Our conclusions are that total adrenalectomy in the cat greatly ameliorates the diabetes following pancreatectomy. In this species, unilateral adrenalectomy does not produce any change.

Further Studies on the Effect of Amebicidal Drugs on Tissue Culture Cells. MARY JANE HOGUE (Anatomical Laboratory, University of Pennsylvania). Tissue cultures were made from the intestines of 8-day-old chick embryos. Locke-Lewis medium was used. The drugs used were arsenious trithio-salicylic acid, carbarsone, kurchi bismuth iodid, proparsamid, and vioform. These were added to Locke-Lewis media in the dilutions 1 to 1000, 1 to 10,000 and 1 to 50,000. The effect of the various dilutions on the tissue culture cells was studied. Arsenious trithio-salicylic acid in all the dilutions was injurious to the tissue culture cells. Carbarsone, diluted 1 to 1000, when it was left on the culture 24 hrs., affected the epithelial cells but not the other cells. In higher dilutions it did not affect any cells. Kurchi bismuth iodid was injurious to all the cells in dilution 1 to 1000. In dilution 1 to 10,000 it did not affect the epithelium but killed or injured the fibroblasts. In dilution 1 to 50,000 the tissue culture cells grew fairly well. Proparsamid in its lower dilutions was injurious to the nerves and slightly injurious to the epithelium. It did not affect the fibroblasts when used for only 24 hrs. Vioform is only slightly soluble in Locke-Lewis solution. The tissue culture cells did not phagocytose it. It was more injurious to the fibroblasts than to the epithelial cells but it affected all the tissues in all the dilutions used.

An Adaptation of the Transparent Chamber Technique to the Skin of the Body. ROY G. WILLIAMS (Anatomical Laboratory, University of Pennsylvania). A skin flap was made in the long axis of a rabbit's body in such a manner that its original bloodvessels and part of its nerves were preserved. This flap was sufficiently long to allow the installation of a transparent chamber and to permit unimpeded observation of the chamber under the microscope. Eight such flaps have been made and chambers installed in 6. Vessels appeared on the table in all cases and grew entirely across in 1. The new tissues from the flap invade the chamber in much the same manner as they do when the chamber is placed in the ear. Such an installation provides an opportunity for comparing the behavior and growth of the tissues in the ear with that in another part of the animal's body.

When the chamber in the flap is provided with a removable top so that direct access to the growth may be had, an opportunity is afforded for implantation of other tissues into the chamber or for direct manipulation of the chamber contents. The exposure of the growing region by removing the top and then replacing it has been done successfully in several cases. A modified chamber designed for this purpose will be described elsewhere.

The Nussbaum Experiment on Renal Secretion. RUDOLF T. KEMPTON (Laboratory of Pharmacology, University of Pennsylvania). When ligation of the renal arteries in American frogs is performed exactly in the manner of the original Nussbaum experiment, urine continues to be excreted after injections of urea. Direct observation of the kidneys of such animals during life showed that the intention of the experiment, complete abolition of glomerular function, had not been realized. Active circulation was observed to persist in the posterior part of the kidneys. Despite ligation of all renal arteries, blood reached the areas supplied by the most posterior of the renal arteries through anastomoses with the distribution of the rectovesical arteries or with the renal portal vein. The volume of this collateral circulation was greatly increased by injections of urea. When this circulation was suppressed by additional ligatures no urine could be obtained from the bladder even after urea injections.

Micro Determination of the pH Fluid in Renal Glomeruli and Tubules. HUGH MONTGOMERY and J. A. PIERCE (Laboratory of Pharmacology, University of Pennsylvania). By administering phenol red subcutaneously or intravenously the colorimetric method of estimation of pH has been adapted for use on 0.2 cmm. of glomerular fluid or tubular fluid. The average error on known solutions is pH 0.03. The method is applicable to plasma when precautions are taken to prevent metabolism of the red cells, and when a constant correction factor is applied.

In the frog the identity of pH of glomerular fluid and plasma was established.

A quinhydrone electrode has been devised for estimation of the pH of 0.02 cmm. of fluid. The average error on known solutions is pH 0.03.

Results by both methods show that the pH of glomerular fluid, of proximal tubular fluid, and of intermediate tubular fluid in Necturus is the same as that of the plasma, and that the decrease in pH takes

place in the distal tubule. The pH of distal tubular fluid was in no case as high as that of the corresponding glomerular fluid, or as low as that of the corresponding urine. No constant relationship between distance down the distal tubule and per cent decrease in pH was demonstrated.

The Sympathetic Control of the Heart. D. W. Bronk, L. K. Ferguson and D. Y. Solandt (Johnson Foundation for Medical Physics, University of Pennsylvania). In order to investigate the activity of the sympathetic motor nerve cells which have an accelerator influence on the heart, and to study the reflex control of this mechanism, we have recorded by means of a vacuum-tube amplifier and oscillograph the efferent impulses in small nerve twigs running from the stellate ganglion to the heart in cats. Normally there is a continuous discharge of impulses which thus provide a constant accelerator influence on the heart. Under certain conditions the impulses are grouped into waves which are synchronous with the pulse and under certain other conditions nervous activity is completely inhibited with each inspiration. Such variations indicate the striking fluctuations which take place in the activity of the sympathetic centers under the influence of various factors, such as the activity of adjoining centers, degree of respiration, nature of the afferent control, and so forth.

As a general rule any rise in mean blood pressure is associated with a decrease or complete inhibition of the sympathetic discharge. This is to a very considerable extent accomplished by way of the afferent impulses going over the carotid sinus and aortic nerves. Distension of a carotid sinus or electrical stimulation of a carotid sinus nerve produces inhibition of the sympathetic efferent discharge for a period which increases with an increase in the degree of afferent stimulation. This reflex is bilateral and simultaneous stimulation of two carotid sinuses produces a summation of inhibitory effect.

Notice to Contributors.—Manuscripts intended for publication in the American Journal of the Medical Sciences, and correspondence, should be sent to the Editor, Dr. Edward B. Krumbhaar, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the American Journal of the Medical Sciences exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the Journal, will be translated at its expense.